University Hospital of North Staffordshire NHS Trust

North Staffordshire Combined Healthcare NHS Trust

Staffordshire and Stoke on Trent Partnership NHS Trust

NHS North Staffordshire Clinical Commissioning Group

NHS Stoke-on-Trent Clinical Commissioning Group

Effective Shared Care Agreement for anagrelide (Xagrid®) in essential thrombocythaemia

AREAS OF RESPONSIBILITY FOR THE SHARING OF 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). 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 total clinical responsibility for the patient for the diagnosed condition remains with the specialist. **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as is practical.**

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

This shared care agreement supports the implementation of The British Committee for Standards in Haematology Society Guideline for investigation and management of adults and children presenting with a thrombocytosis.

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

RESPONSIBILITIES and ROLES

Specialist's responsibilities
1 Confirm the diagnosis and the need for treatment with anagrelide as second line treatment after hydroxycarbamide.
2 Assess likelihood of compliance.
3 Discuss the benefits and side-effects of treatment with the patient as well as the intention to share care.
4 Instruct patient or carer on administration of anagrelide.
5 Ensure the patient is given sufficient information about their treatment.
6 Initiate treatment and prescribe anagrelide until a stable maintenance dose is achieved.
7 Monitor full blood counts, renal function and LFT's at appropriate intervals and regularly review the patient (normally every 2 to 6 months). For very stable patients a telephone appointment may be appropriate (if appropriate commissioning obtained from CCG).
8 Ask the GP whether he or she is willing to participate in shared care and provide GP with a copy of the shared care guideline and supporting information.
9 Advise the GP of the dose and duration of therapy (which is usually long term).
10 Communicate promptly with the GP when treatment is changed or discontinued.
11 Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
12 Inform the GP if the patient does not attend specialist appointments.
13 Report serious adverse events to the CSM and GP where appropriate,
14 Ensure that arrangements exist for GPs to obtain advice and support.

General Practitioner's responsibilities
1 Reply to the request for shared care as soon as practical.
2 Prescribe anagrelide at the dose recommended by the specialist for the treatment duration specified.
3 Adjust the dose as advised by the specialist.
4 Contact the specialist if there are concerns regarding compliance.
5 Report to and seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment.
6 Promptly report any suspected cardiovascular effects to the specialist.
7 Check for possible drug interactions when newly prescribing medication and avoid prescribing interacting drugs.
8 Refer patient back to the specialist if platelet count >$600x10^9$/L or <$100x10^9$/L (discovered incidentally outside regular monitoring).
9 Unless exceptional circumstances discuss with specialist prior to discontinuing treatment.
10 Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
11 Report adverse events to the specialist and serious adverse effects to the CSM.

Patient's/carers role
1 Take anagrelide as recommended by specialist.
2 Report to the specialist or GP if he / she does not have a clear understanding of the treatment.
3 Request repeat prescriptions from the GP at least 5 days before the next supply is needed.
4 Attend scheduled appointments with specialist, GP and for monitoring as detailed above.
5 Share any concerns in relation to treatment with GP or specialist.
6 Report any adverse effects to the specialist or GP.

Monitoring requirements

Monitoring	Full blood count	LFTs	U&Es	GP or Consultant
Baseline	✓	✓	✓	Consultant
Week 1	✓	✓	✓	Consultant
Week 2	✓			Consultant
Week 3	✓			Consultant
Week 4	✓	✓	✓	Consultant
Week 6	✓			Consultant
Week 8	✓	✓	✓	Consultant
Week 10	✓			Consultant
Week 12	✓	✓	✓	Consultant
Every 2 to 6 months thereafter	✓	✓	✓	Consultant

SUPPORTING INFORMATION EFFECTIVE SHARED CARE AGREEMENT

This information should be read in conjunction with the Summary of Product Characteristics for anagrelide (Xagrid®) available from www.medicines.org.uk

Essential thrombocythaemia (ET) is an acquired myeloproliferative disorder characterised by persistent peripheral thrombocytosis and a tendency for thrombosis and haemorrhage. ET can proceed in some case to myelofibrosis, acute myeloid leukaemia (AML), nyelodysplastic syndrome (MDS) or polycythaemia vera (PV).

The estimated annual incidence of ET based on WHO criteria is 1-2.5/100,000 individuals. However, true incidence is likely to be higher as many patients are without symptoms and thus undiagnosed.

ET patients are stratified into risk groups (high, intermediate and low) according to their risk of thrombotic complications.

Studies have shown that cytoreductive therapy in high risk ET patients reduces vascular complications.

Hydroxycarbamide remains first line treatment, but in patients intolerant or refractory to hydroxycarbamide, anagrelide is second line treatment option.

Anagrelide reduces platelet production by inhibiting megakaryocyte colony development, thus reducing megakaryocyte size, ploidy and maturation. Anagrelide has been shown in trials to be as effective as hydroxycarbamide, interferon α and alkylating agents in reducing platelet counts, without the added complication of alkylating or cytotoxic properties.

British Committee for Standards in Haematology: Guideline for investigation and management of adults and children presenting with a thrombocytosis: The BCSH recommends anagrelide and aspirin as second line treatment option for high risk patients with essential thrombocythaemia (>60yrs or platelet count >1500x10^9/L or disease related thrombosis/ haemorrhage).

Indications

- second line treatment of essential thrombocythaemia (ET) in patients who are refractory to treatment with hydroxycarbamide or in whom hydroxycarbamide causes unacceptable depression of haemoglobin and/or WBC

Dosage

The recommended starting dose is 1mg/day, which should be administered in two divided doses (0.5mg/dose).

The starting dose should be maintained for at least one week, after that the dose may be titrated on an individual basis to achieve the lowest effective dose to reduce platelet count to below 600x10^9/L and ideally at levels between 150x10^9/L and 400x10^9/L.

The dose increment must not exceed 0.5mg/day in any one week and the recommended maximum single dose should not exceed 2.5mg. During clinical development doses of 10mg/day have been used.

In most patients in adequate response should be obtained at a dosage of 1-3mg/day.The treatment is usually long term.

Contraindications

- Moderate or severe liver impairment (transaminases > 5 times upper limit of normal). In mild hepatic impairment potential risks and benefits of treatment should be assessed prior to treatment.
- Moderate or severe renal impairment (creatinine clearance < 50ml/min)
- Hypersensitivity to anagrelide or any of the other excipients listed in section 6.1 of the SPC.

Special warnings and precautions for use

Severe cardiovascular adverse events including cases of cardiomyopathy, cardiomegaly, congestive heart failure and cardiac arrhythmias have been reported. Anagrelide should be used with caution in patients of any age with known or suspected heart disease. However, serious cardiovascular events have also occurred in patients with normal pre-treatment cardiovascular examination.

Anagrelide is an inhibitor of cyclic AMO phosphodiesterase III (PDE III) causing positive inotropic effects. A pre-treatment cardiovascular examination is recommended and during treatment patients should be monitored for evidence of cardiovascular effects that may require further investigation.

Anagrelide should only be used if the potential benefits outweigh the potential risks.

Due to the risks of myelofibrotic transformation regular monitoring (3 yearly) for early signs of progression is recommended.

Side Effects

The most common include

- Headache (14-30%)
- Palpitations (9-25%)
- Fluid retention and nausea (6-20%)
- Diarrhoea (5-25%)

Gradual dose titration may help diminish these effects and some may decrease during continued treatment.

Tabulated summary of adverse reactions

Adverse reactions arising from clinical studies, post-authorisation safety studies and spontaneous reports are presented in the table below. Within the system organ classes they are listed under the following headings: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency of Adverse Reactions				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia Pancytopenia Ecchymosis Haemorrhage		
Metabolism and nutrition disorders		Fluid retention	Oedema Weight loss	Weight gain	
Nervous system disorders	Headache	Dizziness	Paraesthesia Insomnia Depression Confusion Hypoaesthesia Nervousness Dry mouth Amnesia	Somnolence Abnormal coordination Dysarthria Migraine	
Eye disorders				Vision abnormal Diplopia	
Ear and labyrinth disorders				Tinnitus	
Cardiac disorders		Palpitations Tachycardia	Congestive heart failure Hypertension	Angina pectoris Myocardial infarction	

			Arrhythmia Atrial fibrillation Supraventricular tachycardia Ventricular tachycardia Syncope	Cardiomegaly Cardiomyopathy Pericardial effusion Vasodilatation Postural hypotension	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis Pleural effusion Pneumonia	Pulmonary hypertension Pulmonary infiltrates	Allergic alveolitis, including interstitial lung disease and pneumonitis
Gastrointestinal disorders		Nausea Diarrhoea Abdominal pain Flatulence Vomiting	Dyspepsia Anorexia Pancreatitis Constipation Gastrointestinal haemorrhage Gastrointestinal disorder	Colitis Gastritis Gingival bleeding	
Hepatobiliary disorders			Hepatic enzymes increased		Hepatitis
Skin and subcutaneous tissue disorders		Rash	Alopecia Skin discoloration Pruritus	Dry skin	
Musculoskeletal and connective tissue disorders			Myalgia Arthralgia Back pain		
Renal and urinary disorders			Impotence	Nocturia Renal failure	Tubulointerstitial nephritis

General disorders and administration site conditions		Fatigue	Chest pain Weakness Chills Malaise Fever	Asthenia Pain Flu-like syndrome	
Investigations				Blood creatinine increased	

Overdose

Post-marketing case reports of intentional overdose with anagrelide have been received. Reported symptoms include sinus tachycardia and vomiting. Symptoms resolved with conservative management.

Xagrid, at higher than recommended doses, has been shown to produce reductions in blood pressure with occasional instances of hypotension. A single 5 mg dose of anagrelide can lead to a fall in blood pressure usually accompanied by dizziness.

A specific antidote for anagrelide has not been identified. In case of overdose, close clinical supervision of the patient is required; this includes monitoring of the platelet count for thrombocytopenia. Dose should be decreased or stopped, as appropriate, until the platelet count returns to within the normal range.

Monitoring

Anagrelide requires regular monitoring which should include full blood count and assessment of serum creatinine and liver function.

Drug Interactions

Limited pharmacokinetic and/or pharmacodynamic studies investigating possible interactions between anagrelide and other medicinal products have been conducted.

Drug interactions: effects of other substances on anagrelide

• 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. Grapefruit juice has also been shown to inhibit CYP1A2 and therefor could also reduce the clearance of Anagrelide.

• *In vivo* interaction studies in humans have demonstrated that digoxin and warfarin do not affect the pharmacokinetic properties of anagrelide.

Drug interactions: effects of anagrelide on other substances

• 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 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.

• *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.

BNF and Chemist &Druggist price excluding VAT

Anagrelide (as hydrochloride) 500 micrograms capsules, net price 100-cap pack = £404.57.

References

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BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Bleep:	Email address:
Specialist in haematology **On-call bleep during working hours** **On-call consultant haematologist during out-of hours** **Relevent Consultant haematologist for a specific patient**	 To contact via Hospital Switch 01782 674285 01782 674284	723	
GP:			
Hospital Medicines Information Dept:	01782 674538		Medicines.Information@uhns.nhs.uk
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