SHARED CARE GUIDELINE FOR PRESCRIBING ANAGRELIDE

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 <400 x 10^9/L. Regular full blood count monitoring is required in order to adjust dosage and to detect progression to myelofibrosis and/or Acute Myeloid Leukaemia (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 remains the first-line treatment for high risk myeloproliferative disorder. Anagrelide has a role in patients who are refractory or intolerant to hydroxycarbamide or in whom hydroxycarbamide causes unacceptable toxicity. It is also chosen by patients with intermediate risk essential thrombocythaemia (ET) who would prefer to avoid using cytotoxic therapy.

It is licensed for the reduction of elevated platelet counts in high risk 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. High risk ET is defined by one or more of the following features:

- > 60 years of age or
- a history of thrombo-haemorrhagic events
- Cardio-vascular risk factors such as previous cardiac or cerebral events, type 2 diabetes, hypertension, peripheral vascular disease

AREAS OF RESPONSIBILITY FOR SHARED CARE

Patients should be at the centre of any shared care arrangements. Individual patient information and a record of their preferences should accompany shared care prescribing guidelines, where appropriate.

Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stable or predictable.

Referral to the GP should only take place once the GP has agreed to this in each individual case, and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that supply arrangements have been finalised. The secondary/tertiary provider must supply an adequate amount of the medication to cover the transition period. The patient should then be informed to obtain further prescriptions from the GP.

When clinical responsibility for prescribing is transferred to general practice, it is important that the GP, or other primary care prescriber, is confident to prescribe the necessary medicines. Shared care agreements play a key role in enabling primary care prescribers to prescribe medicines with which they may not initially be familiar.

Clinical responsibility for prescribing is held by the person signing the prescription, who must also ensure adequate monitoring.

REFERRAL AND INITIATION

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

Specialist Responsibilities	
1	To diagnose essential thrombocythaemia and to decide on treatment
2	Where patients are unable to receive hydroxycarbamide, for example due to intolerance or chronic leg ulcers, to initiate treatment with anagrelide including: • Ensuring the suitability of the patient for anagrelide treatment including performing all relevant pre-treatment assessments (blood tests to include: FBC, LFTs, U&Es and cardiac examination and pregnancy screen if appropriate) • Discussing and agreeing the management strategy with the patient including: ○ informing them of possible side-effects to the treatment and ensuring they are aware of who to contact in this instance ○ ensuring they understand the dosage instructions
3	To monitor full blood counts, review patient (normally every 2-6 months) and titrate dose until platelet count is stable. Very stable patients may receive telephone appointments or may be advised by a nurse practitioner
4	To write to the patient's GP advising them of the treatment commenced, including appropriate prescribing information, dosing increments, the intention to 'share care' unless the specialist team are informed otherwise, ongoing blood monitoring requirements (including who is responsible for checking the results) and arrangements for follow-up
5	To be available for advice if the patient's condition changes and to arrange for the patient to be followed up in the rheumatology out-patient clinic as necessary
6	To arrange monitoring of QT interval and heart function as required

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 >400 x 10^9/L or <100 x 10^9/L (discovered incidentally outside of planned monitoring)
3	To deal with general health issues of the patient
4	To check for possible drug interactions when newly prescribing concurrent medications

Patient's role (or that of carer)	
1	To report to the specialist or GP if he/she does not have a clear understanding of the treatment or is unable to comply with treatment and to report any concerns
2	To attend appropriate consultant and GP appointments
3	To have required monitoring/tests carried out at regular intervals
4	To report any adverse events to the doctor who is prescribing their treatment
5	To take responsibility for appropriate contraceptive precautions

SUPPORTING INFORMATION

Summary of NICE, BNF, SPC or other guidance, where applicable (and a web link to access the full guidance)

Manufactures information (Zentiva) - https://www.medicines.org.uk/emc/product/8981/smpc

Licensed indications & therapeutic class

Essential thrombocythaemia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs.

Anagrelide is an antineoplastic agent.

Dose, route of administration and duration of treatment

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, administered orally in two divided doses. The average daily dose is four capsules (2mg) daily.

Adverse effects (incidence, identification, importance and management)

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

Contraindications

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.

Patients with cardiac insufficiency and arrhythmias

Cautions

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.

In patients of any age with known or suspected heart disease, as serious cardiovascular adverse events such as vasodilation, tachycardia and congestive heart failure have been reported due to anagrelides positive inotropic and chronotropic effects. Caution should also be taken in patients with known risk factors for prolongation of the QT interval. A pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended.

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.

Monitoring requirements and responsibilities

Close monitoring for an effect on the QTc interval is advisable if any cardiac symptoms are reported.

Liver Function Tests: if moderate impairment – starting dose of 0.5mg/day and monitor for cardiovascular effects and hepatic toxicity. If severe impairment – not studied, avoid use.

Platelet counts should be performed regularly to monitor the effect of anagrelide and prevent thrombocytopenia. Typically, platelet counts begin to respond within 7 to 14 days at the proper dosage. Time to complete response ranges from 4 to 12 weeks. Most patients will achieve an

adequate response at a dose of 1.5 to 3 mg daily. Sudden discontinuation or interruption of treatment with anagrelide is followed by an increase in platelet count, usually observed within four days of discontinuation.

Clinically important drug interactions and their management

Increased risk of bleeding events when given with alteplase, factor XA inhibitors, heparins, Omega 3 esters, urokinase, warfarin – manufacturer advises caution or avoid.

Increased risk of QT prolongation with amifampridine, amiodarone, amisulpride, apomorphine, cabozantinib, chlorpromazine, citalopram, clarithromycin, clomipramine, dexamethasone, domperidone, eribulin, erythromycin, escitalopram, flecainide, fluconazole, haloperidol, hydroxyzine, lithium, methadone, ondansetron, pazopanib, quinine, risperidone, sildenafil, sotalol, venlafaxine, voriconazole

Increased risk of hypokalaemia and potentially torsade de pointes with aminophylline, amphotericin, corticosteroids, diuretics, fludrocortisone, ivabradine, salbutamol, terbutaline, theophylline

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

This list is not exhaustive. 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.

Drug costs:

NHS indicative price for 100 x 500mcg capsules = £390.29 at the time of publication (March 2019)

References

BCCA cancer drug manual, *2015*. **Anagrelide**. Available at http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Anagrelide_monograph_1Nov2015.pdf [Accessed 22 Oct 2018]

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Summary of Product Characteristics. Zentiva Pharma UK, *2018*. **Anagrelide Zentiva 0.5mg hard capsules**. Available at: https://www.medicines.org.uk/emc/product/8981/smpc [Accessed 22 Oct 2018]

Written By	Philippa Roe	August 2019
Approved By	Dorset Medicines Advisory Group	July 2020
Date of next review	July 2022 or before, in light of new evidence or information.	