**PACKAGE INSERT TEMPLATE FOR ANAGRELIDE HYDROCHLORIDE CAPSULES**

**Brand or Product Name**
*[Product name]* 0.5mg Capsules

**Name and Strength of Active Substance(s)**

Anagrelide Hydrochloride …..0.5mg

**Product Description**
*[Visual description of the appearance of the product (eg colour, viscosity etc)*
*eg An opaque white hard gelatin capsule imprinted with "X".*

**Pharmacodynamics**
Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III that reduces platelet production and, at higher than therapeutic doses, inhibits platelet aggregation.

**Pharmacokinetics**
*Absorption*
Anagrelide is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 hour after an oral dose on an empty stomach, increasing in the presence of food, although this appears to have no clinically significant effect on bioavailability.
Oral Bioavailability: 75%

*Distribution*
Volume of Distribution: 12 liters/kilogram

*Metabolism*
- It is extensively metabolized in the liver, mainly by the cytochrome P450 isoenzyme CYP1A2.
- Two major metabolites: RL 603 and 3-hydroxy anagrelide.

*Elimination*
Eliminated in the urine; less than 1% of a dose is excreted unchanged. The plasma half-life is about 1.3 hours.
Metabolites are excreted in urine (79%) and faeces (21%). Excretion is >97% complete within 5 days.

## Indication

Anagrelide capsules are indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia 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 one or more of the following features:

- >60 years of age or
- A platelet count >1000 x $10^9$/l or
- A history of thrombo-haemorrhagic events.

## Recommended Dosage

Treatment with Anagrelide capsules should be initiated by a clinician with experience in the management of essential thrombocythaemia.

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

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 below 600 x 109/L and ideally at levels between 150 x 109/L and 400 x 109/L. The dosage increment must not exceed more than 0.5 mg/day in any one week and the maximum single dose should not exceed 2.5 mg.

The effects of treatment with anagrelide must be monitored on a regular basis. If the starting dose is >1 mg/day platelet counts should be performed every two days during the first week of treatment and at least weekly thereafter until a stable maintenance dose is reached.

*Maintenance dose*

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 to 3 mg/day.

*Use in Elderly*

The observed pharmacokinetic differences between elderly and young patients with ET do not warrant using a different starting regimen or different dose titration step to achieve an individual

patient-optimised anagrelide regimen. However, patients in the age group over 60 years of age have higher incidence of serious adverse events (mainly cardiac).

*Use in Children*
Myeloproliferative disorders are uncommon in paediatric patients and limited data are available in this population.

Starting doses in children/adolescent patients have ranged from 0.5 mg/day to 0.5 mg q.i.d. As there are limited data on the appropriate dose for this patient group an initial dose of 0.5 mg/day is recommended.

*Use in Renal Impairment*
Currently, there are no specific pharmacokinetic data for this patient population and the potential risks and benefits of anagrelide therapy in a patient with impairment of renal function should be assessed before treatment is commenced.

*Use in Hepatic Impairment*
Currently, there are no specific pharmacokinetic data for this patient population. However, hepatic metabolism represents the major route of drug clearance so liver function may be expected to influence this process. Therefore it is recommended that patients with moderate or severe hepatic impairment are not treated with anagrelide. The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced.

**Mode of Administration**
Oral

**Contraindications**

- Hypersensitivity to anagrelide or any of the excipients of the medicinal product.
- Patients with moderate or severe hepatic impairment.
- Patients with moderate or severe renal impairment (creatinine clearance <50ml/min)

**Warnings and Precautions**

*Hepatic impairment:* 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).

*Renal impairment:* the potential risks and benefits of anagrelide therapy in a patient with impairment of renal function should be assessed before treatment is commenced.

*Monitoring:* Haemoglobin, white blood cells, and hepatic and renal function should also be monitored until a maintenance dose is established. It is recommended that liver function tests (ALT and AST) are performed before anagrelide treatment is initiated and at regular intervals thereafter.

*Platelets:* Platelet counts should be monitored closely, especially at the start of treatment. Abrupt stoppage of anagrelide therapy may increase platelet counts, usually within 4 days and will return to pre-treatment levels within 10 to 14 days.

*Cardiovascular:* Anagrelide should be used with caution in patients with cardiovascular disease. Cardiac function should be assessed in patients before and during treatment, and patients monitored for cardiovascular adverse effects during treatment.

*Paediatric patients:* limited data are available on the use of anagrelide in the paediatric population and anagrelide should be used in this patient group with caution.

*Effects on the ability to drive and use machines*
Dizziness may affect the performance of skilled tasks such as driving.

**Interactions with Other Medicaments**

There is the theoretical possibility that inhibitors of the cytochrome P450 isoenzyme CYP1A2 could reduce the clearance of anagrelide. Anagrelide itself has limited inhibitory activity towards CYP1A2. Anagrelide may exacerbate the effects of other phosphodiesterase inhibitors such as amrinone, cilostazol, enoximone, milrinone, and olprinone that also produce positive inotropic effects.

Potentiation of the effects of other drugs that modify platelet function when given with anagrelide is a theoretical possibility. Although no clinically significant effects have been seen when given with aspirin to patients with essential thrombocythaemia, enhancement of antiplatelet aggregation effects of anagrelide and aspirin has been reported in a study after co-administration to healthy subjects compared with aspirin alone.

Therefore, before starting concomitant treatment of anagrelide with acetylsalicylic acid (aspirin), the potential risks should be assessed in patients with a high-risk profile for haemorrhage.

Concurrent use of the following drugs with anagrelide may result in an increased risk of bleeding:

- dipyridamole
- aspirin

Concurrent use of the following drugs and antiplatelet agents may result in an increased risk of bleeding:

- milnacipran
- desvenlafaxine
- venlafaxine
- duloxetine
- pentoxifylline

Concurrent use of anagrelide and theophylline may result in increased theophylline serum concentrations and possible theophylline toxicity (nausea, vomiting, palpitations, seizures).

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

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

*Food interactions*

- Food delays the absorption of anagrelide, but does not significantly alter systemic exposure.
- The effects of food on bioavailability are not considered clinically relevant to the use of anagrelide.

**Statement on Usage During Pregnancy and Lactation**

*Pregnancy*
There are no adequate and well-controlled studies with anagrelide in pregnant women. Although a few successful outcomes have been reported where women became pregnant while on anagrelide, the drug is not recommended in women who are pregnant or may become pregnant.

It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If used during pregnancy or if a women becomes pregnant while taking anagrelide, she should be informed of the potential harm to the fetus. Women of child-bearing potential should be cautioned to avoid pregnancy and should be instructed to use contraception while taking anagrelide

*Lactation*
No reports describing the use of anagrelide during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown. It is not known if anagrelide affects the quantity or composition of breastmilk. Until more data are available, a decision should be made whether to discontinue anagrelide therapy or nursing, considering the importance of the drug to the mother

**Adverse Effects / Undesirable Effects**

Adverse effects most commonly reported with anagrelide include headache, palpitations and tachycardia, fluid retention, diarrhoea, nausea, and abdominal pain; fatigue, dizziness, flatulence, vomiting, dyspnoea, rashes, and anaemia have also occurred. Cardiovascular effects also include vasodilatation and positive inotropic effects; myocardial infarction, cardiomyopathy and heart failure have been reported.

Other adverse effects include:

- **Cardiovascular:** atrial fibrillation, cardiomegaly, heart block, hemorrhage, pericardial effusion, pericarditis, thrombosis
- **Gastrointestinal:** loss of appetite , gastrointestinal hemorrhage, pancreatitis
- **Neurologic:** asthenia , cerebrovascular accident, seizure, transient ischemic attack
- **Hepatic:** hepatotoxicity
- **Renal:** renal impairment, tubulointerstitial nephritis
- **Respiratory:** interstitial lung disease, pleural effusion, pulmonary fibrosis, pulmonary hypertension, pulmonary infiltrate

**Overdose and Treatment**

*Symptoms*
Overdose data is limited.
There have been a small number of post-marketing case reports of intentional overdose with anagrelide. Reported symptoms include sinus tachycardia and vomiting. Symptoms resolved with conservative management.

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The signs and symptoms of an acute overdose are expected to be similar to excessive pharmacologic effects (eg, thrombocytopenia, palpitations, abdominal pain, diarrhea, headache).

Should overdosage occur, cardiac and central nervous system toxicity can also be expected. Anagrelide, at higher than recommended doses, has been shown to produce reductions in blood pressure with occasional instances of hypotension. A single 5mg dose of anagrelide can lead to a fall in blood pressure, usually accompanied by dizziness.

*Treatment*
Treatment is symptomatic and supportive.

Close clinical supervision of the patient is required; this especially includes monitoring of the platelet count for thrombocytopenia. Dosage should be decreased or stopped, as appropriate, until the platelet count returns to within the normal range.

**Storage Conditions**
*[eg Store below…. °C ]*

**Dosage Forms and Packaging Available**
*[Packaging type & pack size]*

**Name and Address of Manufacturer**
*[Name & full address of manufacturer]*

**Name and Address of Marketing Authorization Holder**
*[Name & full address of marketing authorization holder]*

**Date of Revision of Package Insert**
*[day/month/year ]*

*Updated September 2013*