Scottish Medicines Consortium

anagrelide 0.5mg capsule (Xagrid®) No. (163/05)

Shire Pharmaceutical Group

4 March 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Anagrelide (Xagrid®) is not recommended for use within NHS Scotland for the reduction of elevated platelet counts in 'at risk' patients with essential thrombocythaemia who are intolerant of their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. The cost effectiveness of anagrelide has not been demonstrated.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Anagrelide 0.5mg capsules (Xagrid®)

Licensed indication under review 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 essential thrombocythemia patient is defined by one or more of the following features: >60 years of age; platelet count >1000 x 10^9/L; or a history of thrombohaemorrhagic events. Treatment with anagrelide should be initiated by a clinician with experience in the management of essential thrombocythaemia.

Dosing information under review 0.5mg twice a day for the first week, then titrated to the lowest dose which reduces and/or maintains a platelet count below 600 x 10^9/L and ideally between 150 and 400 x 10^9/L. Dosage increments should not exceed 0.5mg per day in any one-week and the recommended maximum single dose is 2.5mg. No maximum daily dose is specified, but the summary of product characteristics notes that during clinical development dosages of 10mg per day have been used.

UK launch date January 2005

Comparator medications

Hydroxycarbamide (previously known as hydroxyurea) is also licensed for the treatment of essential thrombocythaemia. Scottish haematologists advise that this is generally the first-line treatment, with anagrelide used second-line for some patients. Other second- and third-line treatments are unlicensed and include interferon, busulfan and radioactive phosphorus.

Cost per treatment period and relevant comparators

	Daily dose range	Annual Cost (£)
Anagrelide	**1-10mg***	**2 460-24 600**
Hydroxycarbamide	1000-2000mg+	628-1 256

* the summary of product characteristics (SPC) notes that doses up to 10mg/day were used in the clinical trials, however, the mean daily dose appears to be about 2mg, this would cost £13.48 per day; + based on a recommended dose range of 15-30mg/kg/day for a 65kg patient

Summary of evidence on comparative efficacy

In an open uncontrolled trial a group of 934 adults with essential thrombocythaemia and platelet count >650 x 10^9/L, comprising the efficacy evaluable population for this condition, were treated with anagrelide titrated to maintain platelet counts below 600 x 10^9/L and preferably between 130 and 450 x 10^9/L. The primary outcome, complete response, was defined as a reduction in platelet counts to ≤600 x 10^9/L or by at least 50% compared with baseline after at least four weeks of treatment, with partial response defined as a reduction of 20% to 49%. A complete response was achieved by 67% of the efficacy evaluable population, with a further 12% having a partial response. In pre-specified analyses response rates for a variety of subgroups, were generally consistent with the response rate for the overall population. The European Medicines Agency European public assessment report (EPAR) for anagrelide notes a further subgroup analysis, which was provided in support of the licensed indication. This appears to have included 725 patients from the efficacy-evaluable population who were intolerant to their previous therapy or whose platelet count could not be controlled by it. Complete and partial response rates in this population were 66% and 11%, respectively.

Complete and partial response rates for the efficacy-evaluable population and pre-specified subgroups of patients with essential thrombocythaemia and platelet count >650 x 10^9/L treated with anagrelide.

		% of responders (95% confidence intervals)		
Population analysed	n	Complete	Partial	Total
Efficacy-evaluable	934	67 (64, 70)	12 (9.4, 14)	79 (76, 82)
Failure to control*[a]	332	69 (64, 74)	10 (6.5, 13)	79 (74, 83)
Treatment intolerant*[b]	290	61 (55, 66)	14 (10, 18)	75 (70, 80)
Extended washout*[c]	182	66 (60, 73)	10 (5.6, 14)	76 (70, 82)
Elevated platelet count*[d]	116	71 (62, 79)	15 (8.2, 21)	85 (79, 92)
Cytoreductive naïve*[e]	161	71 (64, 78)	12 (7.3, 18)	83 (78, 89)

*patients could be included in more than one of these subgroups; a platelet count not controlled with any previous cytoreductive therapy; b not able to tolerate previous cytoreductive therapy; c >30 days between previous cytoreductive therapy and anagrelide; d platelet count >1500 x 10^9/L; e had not received previous cytoreductive therapy and did not receive concomitant cytoreductive therapy in study

A trial co-ordinated by the UK Medical Research Council (MRC) recruited approximately 800 adults with essential thrombocythaemia at high risk, defined as any of the following features: age ≥60 years; platelet count > 1000 x 10^9/L; history of thrombotic, embolic or ischaemic events; haemorrhage related to thrombocythaemia; presence of diabetes or hypertension. They were given aspirin 75mg per day and randomised to also receive anagrelide or hydroxycarbamide. The trial was stopped after a preliminary analysis identified an excess of serious adverse events in the anagrelide group. After a median of 39 months follow-up, intention-to-treat log-rank analyses of time to event indicated that patients treated with anagrelide plus aspirin, compared to those treated with hydroxycarbamide plus aspirin, were significantly more likely to reach the primary composite endpoint, which included arterial thrombosis, venous thrombosis and major haemorrhage: 55 vs. 36 events. Anagrelide plus aspirin was also associated with significantly increased risks of arterial thrombosis, 37 vs. 17 events, and major haemorrhage, 22 vs. 8 events, but a significantly decreased risk of venous thrombosis: 3 vs. 14 events. Long-term control of platelet count was comparable between the two treatment groups.

Number of events and odds ratios from log-rank analyses of time to event in patients with essential thrombocythaemia at high risk of thrombohaemorrhagic events treated with anagrelide plus aspirin and hydroxycarbamide plus aspirin in the MRC-PT1 trial.

	Anagrelide	Hydroxycarbamide	Odds ratio (95% CI)	p-value
Primary composite endpoint*	55	36	1.57 (1.04, 2.37)	0.03
Arterial thrombosis	37	17	2.16 (1.27, 3.69)	0.004
Venous thrombosis	3	14	0.27 (0.11, 0.71)	0.006
Major haemorrhage	22	8	2.61 (1.27, 5.33)	0.008

*includes arterial thrombosis, venous thrombosis and major haemorrhage

Summary of evidence on comparative safety

In the MRC trial, described previously, hydroxycarbamide plus aspirin was better tolerated than anagrelide plus aspirin. Significantly more patients in the anagrelide plus aspirin arm discontinued treatment and the rates of the following types of adverse events were also significantly higher in this treatment arm: cardiovascular, gastro-intestinal, neurological and constitutional. The incidence of myelofibrotic transformation was also significantly higher in this anagrlide group: 16 vs. 5 events, odds ratio (95% confidence interval) 2.92 (1.24, 6.86).

There is ongoing debate about possible increased leukaemic transformation of essential thrombocythaemia with long-term administration of hydroxycarbamide, an alkylating agent. Analysis is confounded by increased use of this drug in combination with other cytoreductive agents in patients with more severe forms of the condition and a causal relationship has not been established. In the MRC trial described previously, transformation to myelodysplastic syndrome or acute myeloid leukaemia occurred six and four times in the hydroxycarbamide plus aspirin and anagrelide plus aspirin groups, respectively. The short follow-up of this study and small number of transformations prevent conclusions about the relative risk of leukaemic transformations with these drugs and this remains uncertain.

Summary of clinical effectiveness issues

In the open-label uncontrolled anagrelide trial described previously 25%, 2% and 2% of all the essential thrombocythaemia patients received concomitant hydroxycarbamide, interferon and busulfan, respectively. About 51% and 24% of those who received hydroxycarbamide, took it for less than one and six months, respectively. In practice, it is possible that benefits obtained with anagrelide monotherapy may be slightly lower than those observed in the trial.

In the open-label uncontrolled anagrelide trial described previously subgroup analysis found a slightly higher response rate in essential thrombocythaemia patients aged 18 to 60 years compared with those aged over 60 years: 82% vs. 77%. Overall safety data indicate that the incidence of adverse effects was slightly higher for patients aged over 65 years compared with those aged 18 to 60 years and the incidence of serious adverse effects was twice as high in the older patient group. Within the older patients, the most commonly reported serious adverse effect was congestive cardiac failure. In practice, the risk/benefit ratio of anagrelide may be better for younger patients than for older patients.

Summary of comparative health economic evidence

Two published economic studies with USA unit costs were submitted in support of the above indication.

One study presents the cost per effect of each 3-month block period up to 1-year. The absence of a comparator arm (either direct or indirect) makes this study inappropriate for an assessment of cost-effectiveness for the above indication.

The second study presents the incremental cost per life year gained comparing three different treatment strategies; where anagrelide is considered as either 1st, 2nd or 3rd line therapy. It is difficult to extrapolate the results of this study, to the above indication and a UK/Scotland context**.** This study shows the cost-effectiveness ratio of anagrelide compared to hydroxycarbamide to be sensitive to a reduction in hydroxycarbamide lifetime leukaemia risk (from 0.10 to 0.05), increasing the Incremental Cost Effectiveness Ratio from $72,000 to $156,969.

Budget impact

The budget impact is based on a median daily dose of four capsules per day, an average daily treatment cost of £13.50 corresponding to an annual treatment cost of £5,000

The budget impact assumes a gross cost of £275,500, £389,000, £502,000, £566,000 and £630,000 for years 2005-2009, respectively based on a predicted penetration of anagrelide of 10%, 14%, 18%, 20%, 22% for years 2005-2009.

Additional information

The European Medicines Agency designated anagrelide as an orphan medicinal product on 29th December 2000. It has been available for the treatment of thrombocythaemia within Europe on compassionate “off-label” use for a number of years.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 8 February 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

Shire Pharmaceuticals. Study Report No. 13970-301. An open protocol for the use of Agrylin® (anagrelide hydrochloride) for patients with thrombocythaemia. 5th March 2002.

European Medicines Agency. European public assessment report for XagridÒ. www.emea.eu.int/humandocs/Humans/EPAR/xagrid/Xagrid.htm

Green A, Campbell P, Buck G et al. The Medical Research Council PT1 trial in essential thrombocythaemia. Abstract number 6 presented that the American Society of Hematology 46th annual meeting on 4-7 December 2004, San Diego.