Scottish Medicines Consortium

Re-Submission

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

Shire

09 September 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 resubmission

Anagrelide (Xagrid®) is accepted 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.

Anagrelide reduces platelet counts in patients with essential thrombocythaemia who were intolerant of another cytoreductive therapy or whose platelet count could not be controlled by it.

Overleaf is the detailed advice on this product.

Chairman, Scottish Medicines Consortium

Anagrelide 0.5mg capsule (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 thrombocythaemia 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 that reduces and/or maintains a platelet count below 600 x 10^9/L and ideally between 150 and 400 x 10^9/L. 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 – 10 mg***	**2461 - 24611**
Hydroxycarbamide	1000 – 2000 mg[+]	87 - 174

costs from eVadis database accessed on 6th July 2005; * 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, which would cost £4922 per year; + based on a recommended dose range of 15-30mg/kg/day for a 65kg patient.

Summary of evidence on comparative efficacy

Anagrelide reduces platelet formation by inhibiting maturation of megakaryocytes, reducing their size and ploidy. The exact mechanism of this is not understood. It inhibits cyclic AMP phosphodiesterase III enzyme, but the role of this in reducing platelet numbers is not known.

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 given 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. These are detailed in the table below. The European Medicines Agency's 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 809 adults with essential thrombocythaemia at high risk of vascular events, with 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 essential thrombocythaemia; presence of diabetes or hypertension, which require drug therapy. About a third of study population had been previously treated with cytoreductive drugs; about a half had previously received only aspirin or another anti-platelet drug and the remaining 18% were treatment-naive. They were randomised to anagrelide or hydroxycarbamide and all patients were given aspirin 75mg (100mg in Australia) daily, with the protocol recommending that initiation of aspirin be delayed in patients with very high platelet counts. The trial was stopped when an interim analysis identified an excess of 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 given anagrelide plus aspirin, compared to those given 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. These results are detailed in the table below. Platelet count was comparable in the two groups from nine months, but was significantly lower in the hydroxycarbamide group compared to the anagrelide group at three and six months.

Number of events and odds ratios from log-rank analyses of time to event in patients with essential thrombocythaemia at high risk of vascular events given anagrelide plus aspirin and hydroxycarbamide plus aspirin.

	Anagrelide / aspirin (n=404)	Hydroxycarbamide/ aspirin (n=405)	Odds ratio (95% CI)	p-value
	Number of patients			
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 group discontinued treatment due to adverse effects, 88 vs. 43, and the rates of the following adverse events were significantly higher in this group: nonthrombotic cardiovascular; gastro-intestinal; headache and constitutional. Also, the incidence of myelofibrotic transformation was significantly higher in the anagrelide plus aspirin group: 16 vs. 5 events, odds ratio (95% confidence interval (CI)): 2.92 (1.24, 6.86). The incidences of leg ulcers and mouth ulcers were significantly increased in the hydroxycarbamide plus aspirin group. These results are detailed in the table below.

Adverse effects occurring at significantly different rates in patients with essential thrombocythaemia given anagrelide plus aspirin or hydroxycarbamide plus aspirin

	Hydroxycarbamide/ aspirin (n=404)	Anagrelide / aspirin (n=405)	p-value
Nonthrombotic cardiovascular events	27	92	<0.001
Palpitations	7	63	<0.001
Gastrointestinal events	36	59	0.01
Diarrhoea	6	18	0.01
Abdominal pain	1	9	0.008
Headache	8	51	<0.001
Noncardiac oedema	5	25	<0.001
Constitutional symptoms*	12	41	<0.001
Dermatological events	45	29	0.05
Leg ulcer	20	9	0.04
Mouth ulcer	8	1	0.02

* includes fatigue, weight change, fevers, flushing, sleep disturbance and loss of appetite.

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: odds ratio (95% CI): 0.67 (0.20, 2.33). There was no significant difference between the two groups, but the short follow-up of this study and small numbers of transformations prevent conclusions about the relative risk of leukaemic transformations with these drugs and this remains uncertain.

Summary of clinical effectiveness issues

The MRC trial clearly demonstrated superiority of treatment with hydroxycarbamide to treatment with anagrelide, this leading to the licensed indication for anagrelide being use in patients intolerant of or not adequately controlled by first-line therapy.

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 older patients, the most commonly reported serious adverse effect was congestive cardiac failure. Therefore, the risk/benefit ratio of anagrelide may be better for younger patients than for older patients.

Summary of comparative health economic evidence

The economic evaluation was a decision model comparing second line use of anagrelide with interferon-alfa therapy and with no therapy in a hypothetical woman aged 60 with essential thrombocythaemia. The main data were derived from a literature search of studies that reported response rate (platelet count < $450x10^9$/L) for either anagrelide , interferon-alfa or no therapy but excluded the main phase III long term open label clinical trial of anagrelide. A Markov model was used to model transition between complication-based health states, through to death.

A cost-per-QALY of £14,800 versus interferon-alfa and £28,000 versus no therapy was estimated by the manufacturer. Sensitivity analysis suggests a 53% probability of cost effectiveness at a willingness-to-pay threshold of £30,000. Anagrelide is an orphan drug.

Budget impact

The manufacturers estimate a budget impact of £255,000 in 2006 (based on 60% of eligible patients receiving anagrelide), up to a maximum of £463,400 (by 2010) if all essential thrombocythaemia patients eligible for second line treatment were to receive anagrelide. However, this appears to cover all patients with essential thrombocythaemia, not just those at-risk or woman aged at least 60 years in line with the patients included in the economic model, therefore this is likely to be an overestimate.

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.

After review of a full submission the Scottish Medicines Consortium issued advice on 11th April 2005 that anagrelide 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. Anagrelide reduces platelet counts in patients with essential thrombocythaemia. However, in patients at high risk of thrombohaemorrhagic complications, anagrelide plus aspirin was associated with a higher risk of these events compared to hydroxycarbamide plus aspirin. The cost effectiveness of anagrelide has not been demonstrated.

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 22 August, 2005.

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

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Harrison CN, Campbell PJ, Buck G et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 2005; 353: 33-45.