Scottish Medicines Consortium

vinorelbine 20 and 30mg capsules (Navelbine® Oral) No. (179/05)
Pierre Fabre Ltd

06 May 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

Vinorelbine capsule (Navelbine®Oral) is accepted for restricted use within NHS Scotland for the first line treatment of stage lll or lV non-small-cell lung cancer. It is restricted to use by specialist oncologists as an alternative to the intravenous formulation of vinorelbine. It is more expensive than the intravenous formulation of vinorelbine. However, its use may allow changes to service delivery that have individual patient or organisational benefits.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Vinorelbine oral 20 and 30mg capsules (Navelbine® Oral)

Licensed indication under review

As a single agent or in combination for the first line treatment of stage lll or lV non-small-cell lung cancer.

Dosing information under review

As a single agent 60mg/m^2 of body surface area, administered once weekly for the first three administrations then increased to 80mg/m^2 once weekly except in patients for whom the neutrophil count dropped once below 500/mm^3, or more than once between 500 and 1000/mm^3 during the first three administrations of 60mg/m^2. For combination therapy, the dose and schedule should be adapted to the treatment protocol.

Date of licensing or licence status on the date of review

March 2005

UK launch date

16 May, 2005

Comparator medications

Vinorelbine IV, gemcitabine, paclitaxel, docetaxel

Cost per treatment period and relevant comparators

Drug	Dose (for day 1 and 8 in 21 day cycle)	Cost of 1 cycle	Cost of 4 cycles
Vinorelbine Oral	60-80mg/m^2	£484-616	£1,936-2,332
Vinorelbine IV	25-30mg/m^2	£280-340	£1,120 - £1,360

Basic NHS costs based on body-surface area (BSA) of 1.7m^2 (quantities were adjusted to the nearest 10mg) and MIMS February 2005 prices. Oral vinorelbine cost is based on the company estimate of £2.199 per mg. SIGN guidelines recommend combination therapy with platinum-based chemotherapy where tolerated (not shown).

Summary of evidence on comparative efficacy

Vinorelbine IV was launched in the UK in June 1997 and is a standard treatment in Scotland for advanced non-small-cell lung cancer (NSCLC). An oral formulation of vinorelbine has now been developed, and licensed as a line extension to the existing IV formulation. Vinorelbine oral has linear pharmacokinetics at therapeutic doses and an absolute bioavailability of around 40% which is not affected by food. Bioequivalence studies have shown that oral vinorelbine administered at 60mg/m^2 and 80mg/m^2 is equivalent to 25mg/m^2 and 30mg/m^2 of the IV formulation, respectively. Inter- and intra-individual variability is similar after administration by IV and oral routes.

Several phase ll studies have compared oral with IV vinorelbine both as monotherapy and in combination with cisplatin or carboplatin as first line therapy in advanced, inoperable NSCLC. The primary endpoint in all trials was overall tumour response rate (ORR) in the intention to treat population with secondary outcomes that included duration of response, progression-free survival (PFS), overall survival, as well as evaluation of treatment toxicity, quality of life and clinical benefit. The main supportive trial for this new formulation was a dose escalation study in 115 previously untreated patients with stage lllb or IV NSCLC. Patients were randomised 2:1 to oral vinorelbine 60mg/m^2/week for three administrations with escalation to 80mg/m^2/week thereafter if there was no severe neutropenia (n=77), or vinorelbine IV 30mg/m^2/week (n=38). Treatment was continued until evidence of disease progression, excessive toxicity or patient refusal. No primary anti-emetic prophylaxis was used in this trial. The aim of this trial was to evaluate activity and safety of oral vinorelbine against IV vinorelbine but it was not designed to allow for statistical comparison between treatment arms. There were nine partial responses (PR) in the oral group giving an ORR of 12% (95%CI; 5-19%) and four in the IV group, ORR 11% (95%CI;1-20%). The median PFS was 3.2 and 2.1 months, median duration of response 7.7 months and 5.5 months and the median overall survival 9.3 months and 7.9 months, for the oral and IV formulations respectively. In the oral arm, 58 of 68 patients had their dose increased to 80mg/m^2, 13 subsequently had a dose reduction and then six had a further dose escalation.

The other two monotherapy trials were non-randomised, conducted in elderly patients and although the ORR was significantly lower in one trial the outcomes for median duration of response and survival were similar to previously reported.

Three trials in a total of 158 patients with advanced NSCLC have evaluated oral vinorelbine in combination with cisplatin. In the first trial (n=56), cisplatin 100mg/m^2 was given on day 1 of every three-week cycle with vinorelbine IV 25mg/m^2 given on day 1 followed by vinorelbine oral 60mg/m^2/w thereafter. Treatment was planned for eight cycles. In the second trial (n=56), patients received four 21-day cycles of cisplatin 80mg/m^2 on day 1 in combination with oral vinorelbine 60mg/m^2 on days 1 and 8 in cycle 1, then subsequently with vinorelbine 80mg/m^2 on days 1 and 8 from cycles 2 to 4; followed by consolidation therapy with oral vinorelbine 60mg/m^2/week for the first 3 weeks then escalated to 80mg/m^2/week for patients who had achieved an objective tumour response, or stable disease. In the third trial (n=46) oral vinorelbine 60mg/m^2 was administered on days 1 and 8 of each 21-day cycle in combination with cisplatin 80mg/m^2 on day 1 of each cycle. There were 17, 13 and 15 partial responses in the three trials respectively, giving ORRs of 30% (95%CI; 18-42%), 23.2% (95%CI; 13-36%) and 33% (95%CI; 19-48%) and progression free survival of 5.5 months, 4.2 months and 5 months

One trial in 52 patients evaluated a 3- weekly cycle of carboplatin (dose to provide an AUC of 5mg/ml/min on day 1) in combination with vinorelbine IV 25mg/m^2 on day 1 and oral vinorelbine 60mg/m^2 on day 8. Treatment was planned for eight cycles. A partial response was achieved in eight patients giving an ORR of 15% (95%CI; 5.6-25%). The median progression-free survival was 5.1 months, and median survival 9.3 months.

Summary of evidence on comparative safety

Vinorelbine IV has been available in the UK for almost eight years and its safety profile is well established. The safety profile of oral vinorelbine is qualitively similar to that observed with IV vinorelbine; it is, in general, well tolerated.

In the key trial, the incidence of nausea and vomiting in the oral arm increased proportionally with dose (overall incidence 83% and 65%, respectively); with grade 3-4 nausea reported in 11% of patients and vomiting in 8% of patients compared with 0% and 3% in the IV arm,

respectively. However, anti-emetic prophylaxis was not routinely prescribed during this trial nor was the medication taken with food. Oral vinorelbine has since been classified as an intermediate risk drug for acute emesis, with the use of anti-emetics recommended in all subsequent trials, resulting in a reduction in the incidence of reported grade 3-4 nausea and vomiting.

The substitution of IV by oral vinorelbine in combination with cisplatin or carboplatin did not significantly change the tolerance profile of vinorelbine with platinum compounds.

Summary of clinical effectiveness issues

The pharmacokinetic properties of oral vinorelbine were established in phase l trials with the bioequivalence between oral and IV doses calculated. There have been seven further phase ll clinical studies, but only one of these had a comparative arm, which lacked statistical analysis, and therefore equivalence/non-inferiority has not been statistically confirmed. This one randomised trial directly compared oral with IV vinorelbine monotherapy and did show similar efficacy and tolerability between the two formulations. All of the other six trials were of open, non-comparative design. Although not robust, comparison of the outcomes from the above trials with previously published trials of IV vinorelbine, both as monotherapy and in combination with both cisplatin and carboplatin in patients with NSCLC, found the outcomes to be similar.

The availability of an oral formulation of vinorelbine with similar efficacy to the IV formulation may offer the patient choice, provide greater convenience and lead to less time spent on hospital visits. There could be advantages in convenience for clinical staff and some savings in time also.

Summary of comparative health economic evidence

The manufacturer submitted an economic model comparing oral vinorelbine with IV vinorelbine, paclitaxel, docetaxel and gemcitabine for three different patient management regimens (a combination of daycare in hospital, outpatients and self-administered at home). The model assumed the drugs were of equivalent clinical effectiveness but tolerances and adverse events were modelled separately.

The model demonstrated that oral vinorelbine may be cost effective as monotherapy. However, the model assumed that efficiencies in service delivery would be realised i.e. patients will move from daycare within a hospital setting to an outpatient setting. In addition, the model does not include combination therapy, which will also influence how much efficiency can be achieved.

Budget impact

The manufacturer estimates that direct drug costs would rise by about £200,000 if 300 patients were to switch to oral vinorelbine from IV vinorelbine for monotherapy as well as a range of combination therapies.

Guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) have just published updated guidance on the *Management of patients with lung cancer*. SIGN No 80. February 2005. In the guidance, vinorelbine was found to be effective as monotherapy and was recommended as one of four options (along with gemcitabine, paclitaxel and docetaxel) in combination with platinum agents in advanced NSCLC. It also states that selected older patients should be offered chemotherapy and that the number of cycles administered in advanced disease should not exceed four.

The National Institute of Clinical Excellence (NICE) Clinical Guideline 24. Lung Cancer. The diagnosis and treatment of lung cancer published in February 2005 states that chemotherapy should be offered to patients with stage III and IV NSCLC and good performance status to improve survival, disease control and quality of life. Chemotherapy for advanced NSCLC should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Patients unable to tolerate a platinum combination may be offered single agent chemotherapy with a third generation drug.

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 14 April 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.

References

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