All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Vinorelbine (Navelbine®) capsules
Pierre Fabre Limited

Advice No: 1007 – October 2007

Recommendation of AWMSG

Oral vinorelbine (Navelbine®) is recommended for use within NHS Wales as a single agent (in line with current NICE recommendations for IV vinorelbine), for the treatment of advanced breast cancer stage III and IV relapsing after or refractory to an anthracycline-containing regimen.

Oral vinorelbine (Navelbine®) should only be initiated by specialists experienced in the treatment of breast cancer.

Oral vinorelbine (Navelbine®) should not presently be recommended for shared care.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

Date: 18th October 2007

The recommendation of AWMSG is:

Oral vinorelbine (Navelbine®) is recommended for use within NHS Wales as a single agent (in line with current NICE recommendations for IV vinorelbine), for the treatment of advanced breast cancer stage III and IV relapsing after or refractory to an anthracycline-containing regimen.

Oral vinorelbine (Navelbine®) should only be initiated by specialists experienced in the treatment of breast cancer.

Oral vinorelbine (Navelbine®) should not presently be recommended for shared care.

Key factors influencing the recommendation:

- From the studies available oral vinorelbine (Navelbine®) is an active agent and is relatively well tolerated in advanced breast cancer.
- AWMSG has concerns that there is no comparative evidence between the vinorelbine formulations in the treatment of breast cancer.
- Based on the assumption that the oral formulation of vinorelbine (Navelbine®) has a similar pharmacokinetic profile to the intravenous preparation, the oral formulation of vinorelbine would appear to be cost-effective.
- AWMSG suggests that oral vinorelbine (Navelbine®) should only be used in the context where IV vinorelbine is appropriate for use.
- From the patients' perspective there are obvious advantages of an oral formulation.

2.0 PRODUCT DETAILS:

2.1 Licensed indication[1]:
Oral vinorelbine (Navelbine®) is licensed as a single agent or in combination, for the treatment of advanced breast cancer stage III and IV relapsing after or refractory to an anthracycline-containing regimen.

2.2 Dosing[1]:
As a single agent, the recommended regimen involves a dose of 60mg/m² of body surface area (BSA), taken orally once weekly for the first three administrations. The dose of subsequent administrations should then be increased to 80mg/m² BSA once weekly except in those 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 at 60mg/m² BSA.

Capsules of different strengths (20 and 30mg) are available in order to choose the adequate combination for the right dosage. Further information regarding the administration of oral vinorelbine can be found in the Summary of Product Characteristics[1].

2.3 Market authorisation date: 26th June 2007

2.4 UK Launch date: No formal launch date anticipated.

3.0 DECISION CONTEXT
Breast cancer is the second most frequent cancer in the world and is by far the most common malignant disease in women[2]. Between 16 to 20 percent of people initially presenting with breast cancer have advanced disease with distant metastases, and around half of those presenting with early or localised breast cancer will eventually develop metastatic disease [3,4]. It is currently considered incurable; surgery at this stage would be palliative [2]. Prognosis depends on age, extent of disease, and oestrogen receptor status. There is also evidence that over-expression of the human epidermal growth factor receptor 2 (HER2) which occurs in about 15 to 20 percent of women with metastatic breast cancer, is associated with a worse prognosis[3].

The choice of therapy is influenced by the rate of progression and distribution of the disease and by whether the drugs have already been used as adjuvant therapy. Systemic chemotherapy is considered the first line treatment of choice for patients with advanced or metastatic breast cancer resistant to hormonal manipulation, those who are oestrogen receptor-negative, or those with rapidly growing visceral disease [3,4].

Anthracyclines are still considered to be among the most active agents for the treatment of breast cancer and are a component of many adjuvant and palliative regimens. However, the clinical usefulness of these agents can be limited by their toxicity profiles, in particular their cardiotoxicity which also limits the total cumulative dose that can be given [5]. The taxanes have an established role as a second line treatment in metastatic breast cancer, especially in people with disease progression despite a previous anthracycline based regimen [2,5]. Capecitabine currently occupies a place as third line therapy after failure of anthracyclines and taxanes in competition with vinorelbine [3,5]. The potential for enhanced or synergistic activity with the use of targeted biologics, such as trastuzumab in combination with traditional chemotherapy agents is also under investigation [4].

A number of studies have investigated intravenous vinorelbine in metastatic breast cancer as first line therapy [6-9] and alone or in combination in patients with anthracycline pre-treated disease [5]. In December 2002 the National Institute for Health and Clinical Effectiveness (NICE) issued guidance on the use of intravenous (IV) vinorelbine for the treatment of advanced breast cancer. Vinorelbine (IV) is currently recommended as one option for second line or later therapy for the treatment of advanced breast cancer when anthracycline containing regimens have failed or are unsuitable [10]. This guidance will be updated and incorporated into the advanced breast cancer guideline, which is due for publication in 2009[11] (refer to section 9.3).

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

From the studies available vinorelbine is clearly an active agent and is relatively well tolerated in advanced breast cancer. However, review of the safety data from trials has demonstrated a significant dose dependent neutropenia. Although this is a common chemotherapy-related toxicity it does require close haematological monitoring to achieve maximum tumour response while avoiding haematological toxicity. In the studies submitted oral vinorelbine was mostly used as a first line therapy in advanced disease and the majority of patients had not received prior anthracycline based chemotherapy. This does not fit with the current NICE guidance where vinorelbine (IV) monotherapy is recommended as one option for second line or later therapy for the treatment of advanced breast cancer when anthracycline based regimens have failed or are unsuitable.

Presently, the use of oral vinorelbine is limited by the lack of randomised, controlled trials and comparative data. Nevertheless, in view of its relatively milder toxicity profile, elderly and/or frail patients or those prioritising other aspects of quality of life may choose vinorelbine over more established cytotoxic agents. Further well-designed prospective studies are needed in order to provide more information on safety, tolerability and the optimal dose especially in patients with pre-treated metastatic breast cancer. They should include randomised studies comparing intravenous with oral vinorelbine to confirm equivalent efficacy and safety profiles. Further studies investigating the value of oral vinorelbine in combination therapy in general are also required, along with comparative clinical trials to help clarify the place of oral vinorelbine in the management of advanced breast cancer.

4.2 Review of the evidence on cost-effectiveness

There are some concerns over the use of cost-minimisation analysis especially given the lack of a direct comparison and differences in the adverse event profiles. However, the model does take into consideration the potential additional resource implications resulting from the use of anti emetics and uses an expensive treatment to demonstrate the overall cost difference between the two routes of administration.

From the patients' perspective there are obvious advantages of an oral formulation, which might be offset by the increased incidence of adverse events. Assuming that the oral formulation regimen is similar to the IV regimen, then it is reasonable to suppose that the oral formulation of vinorelbine would be cost-effective relative to IV vinorelbine.

If the most likely treatment regimen were implemented there would be a saving of between £800 and £2600 per patient switched to oral vinorelbine. The company has estimated that, on the basis of 75 patients in Wales being switched to oral vinorelbine, there would be a net saving of between £92,000 and £131,000 per year.

5.0 LIMITATIONS OF DECISION CONTEXT:

- Pharmacokinetic studies have shown bio-equivalence between the oral and IV preparations of vinorelbine, but at this time there is no published efficacy and safety data that directly compares oral vinorelbine to IV vinorelbine, although qualitatively they appear to be similar.
- Further well-designed prospective studies are needed in order to provide more information on safety, tolerability and the optimal dose especially in patients with pre-treated metastatic breast cancer and should include randomised studies comparing IV with oral vinorelbine to confirm equivalent efficacy and safety profiles.
- In the studies submitted oral vinorelbine was mostly used as a first line therapy in advanced disease and the majority of patients had not received prior anthracycline based chemotherapy. This does not fit with the current NICE guidance where vinorelbine (IV) monotherapy is recommended as one option for second line or later therapy for the treatment of advanced breast cancer when anthracycline based regimens have failed or are unsuitable.
- Further studies investigating the value of oral vinorelbine in comparative clinical trials (including taxanes) would also help clarify the place of oral vinorelbine in the management of advanced breast cancer.
- The assumption that the oral formulation regimen is similar to the IV regimen is pivotal in informing the cost effectiveness decision.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

The company state that throughout the UK, the majority of breast cancer patients suitable for treatment with vinorelbine receive it as a monotherapy [12].Their submission is based on two monotherapy studies [13-15] conducted by the company, along with two independent studies, which have been published recently [16,17]. All four are phase II studies. Although currently NICE do not recommend the use of vinorelbine in combination therapies[10], a further three phase II studies (two in abstract) have also been submitted on the use of oral vinorelbine in combination with other chemotherapy, for completeness [18-20].

6.1.1 Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy (CA206) [13,15]

The purpose of the study was to evaluate the efficacy, tolerance and pharmacokinetic profiles of oral vinorelbine given as first line chemotherapy for locally advanced or metastatic breast cancer.

Patients aged between 18 to 75 years with histological confirmed advanced breast cancer were eligible if they had: received no previous chemotherapy for locally advanced disease or metastatic breast cancer, clear evidence of progression after one or more hormonal treatments for advanced disease, presence of at least one bi-dimensionally measurable lesion and a World Health Organisation (WHO) performance status of two or less. Adjuvant chemotherapy was allowed if completed at least 12 months before study entry, as was adjuvant hormonal treatment. Male patients were not eligible for the study and neither were females with the following exclusion criteria: inflammatory breast cancer, prior chemotherapy for advanced breast cancer, prior treatment with vinca alkaloids, concurrent treatment with experimental agents, and previous or current malignancies. A complete list of inclusion/exclusion criteria can be found by referring to the publication by Freyer and colleagues [13].

This was an open label, multicentre phase II trial involving 64 patients who received oral vinorelbine once weekly for a total of eight weeks, unless progression or toxicity occurred. Patients who achieved a response or no change continued to receive weekly treatment as tolerated, and were re-evaluated every 4 weeks [10]. Oral vinorelbine was given at 60 mg/m^2 BSA weekly for the first three administrations and was increased to 80 mg/m^2 BSA for the subsequent administrations if there was no grade IV neutropenia or not more than one episode of grade III neutropenia.

The primary endpoint measured was tumour response, which was assessed using the standard WHO criteria [21] at the time of the study, with modifications suggested by the EORTC [22]. Complete response (CR) was defined as complete disappearance of disease for at least four weeks without appearance of a new lesion. Partial response (PR) consisted of 50% or greater reduction in the sum of the size of all measurable lesions for at least four weeks without appearance of a new lesion or progression of any lesion. Progressive disease (PD) was defined as the appearance of a new lesion or an increase of 25% or greater in the sum of the size of any measurable lesion. No change (NC) was a change insufficient to qualify for PR or PD.

In order to be included in the efficacy data, a patient had to receive at least four administrations within eight weeks. All tumour responses had to be confirmed by re-documentation with the same investigations after four weeks and validated by an independent panel review.

Secondary endpoints included: tolerability of treatment, effect on quality of life, time to progression, and progression free survival. Adverse events were graded according to National Cancer Institute common toxicity criteria (NCI-CTC) [23]. Quality of life was measured with the validated QLQ-C30 questionnaire at study entry and eight weeks later [12].

Results:
From the trial, a median of nine doses (range: 1 to 56), were given over a median treatment length of 10.4 weeks (range: 1 to 77). Six patients were considered ineligible or unevaluable for response because of reasons highlighted by Freyer and colleagues [12,24]. Of the 58 patients evaluated for best response, four (6.9%) demonstrated a CR, 14 (24.1 %) a PR, 18 NC and the disease was found to have progressed in over one third (37.9%, 22 out of 58). The overall response rate was 31 % (95% CI, 19% to 43%), with a median duration of response of 38.1 weeks. In the intent-to-treat (ITT) population (64 patients), the overall response rate was 30% (95% CI, 18% to 41%). Median progression free survival was 17.4 weeks (range not given).

The number of completed questionnaires available for analysis of quality of life had decreased dramatically by the third and fourth evaluations. Consequently analysis was limited to a small number of sets containing baseline, first and second evaluations. No significant change in functional status was reported.

Points to note from this study:
- There were no UK centres included in this trial.
- Of the 30 patients who prematurely discontinued the trial due to disease progression, eight had initially been documented as having a response or no change before disease progression was subsequently reported.
- Further observations on this study are highlighted along with the study by Amadori and colleagues, and summarised below (section 6.1.2).

6.1.2 Phase II study of oral vinorelbine in first-line metastatic breast cancer chemotherapy (CA201) [14,15, 25]

This was a second open label, multicentre, phase II study carried out simultaneously by the company. It assessed the clinical efficacy and tolerability of oral vinorelbine as a single agent in the first line treatment of metastatic breast cancer, given once weekly as in the first study conducted by Freyer and colleagues (section 6.1). The same inclusion/exclusion criteria and dose modification procedures from the previous trial (section 6.1.1) were used.

In this study, 72 participants were enrolled and then stratified by category: prior adjuvant hormonotherapy, prior adjuvant chemotherapy followed or not by adjuvant hormonotherapy, or no prior adjuvant therapy. The duration of treatment was at least eight weeks unless disease progression and/or there was excessive toxicity. Patients maintaining a response at week 12 could continue with oral vinorelbine on a fortnightly basis according to the physician's discretion. Those with stable disease at week eight continued on a weekly regimen for a further three months.

Assessment of efficacy, safety, pharmacokinetics and quality of life was carried out as in the previous trial conducted by Freyer and colleagues, with the primary endpoint being tumour response determined according to the WHO criteria completed by EORTC definitions. Median overall survival was also calculated in the study.

Results:

With regards to treatment administration, there was a median value of 13 doses (range: 1-111) given over a median treatment length of 16.4 weeks (range: 1 to 112). Five patients prematurely discontinued the study before dose escalation, two due to drug related serious adverse reactions (SAE). Of the 67 remaining, only 57 patients received the escalated dose of 80mg/m^2 BSA. This was because six patients remained on the lower dose due to grade III or IV neutropenia as per protocol and four patients received all administrations at a dose of 60mg/m^2 BSA without specific reason. The dose was subsequently reduced from 80mg/m^2 to 60mg/m^2 in 17 patients and then re-escalated in five of them. Overall, dose delays of greater than three days were reported in 54 out of the 70 patients (77%) who had received more than one course.

The four patients who remained on the lower dose of 60mg/m^2 BSA for no specific reason were considered to have violated the protocol therefore only 63 patients were evaluated for efficacy. In the overall population, two patients achieved a complete response and 17 achieved a partial response, yielding a response rate of 26.4% (95% CI: 16 to 37) in the ITT population and 30% (95% CI: 19 to 41) in the evaluable patients. The median duration of response in the 19 respondents was 6.7 months (95% CI: 4.6 to 12.2 months). Median progression-free survival was 4.6 months (95% CI: 4 to 6.6 months). Median overall survival was calculated as 20.7 months (95% CI: 17.4 to 37.3 months).

Points to note from both studies (sections 6.1.1 and 6.1.2):

- In both studies oral vinorelbine was used as a first line therapy for advanced disease and the majority of patients had not received prior anthracycline based adjuvant chemotherapy. This is different to the current NICE guidance where vinorelbine (IV) monotherapy is recommended as one option for second line or later therapy for the treatment of advanced breast cancer when anthracycline based regimens have failed or are unsuitable [10].

- In general, the baseline patient demographics between these two trials were similar. The median age of 63 years was the same, but there were a larger percentage (81% vs. 96%) of patients with metastases and slightly more patients had received prior adjuvant or neoadjuvant therapy in the second (CA201) compared to the first (CA206) study (40% vs. 31% respectively). In both studies, less than one fifth of patients had received prior adjuvant chemotherapy that was anthracycline based. The median disease-free interval prior to study entry was greater for participants in the second (CA201) trial (48 vs. 29.3 months) and more patients had a WHO performance status of zero (68% vs. 48%).
- Overall, the tumour response rate was similar when comparing the first and second trial (30% vs. 26.4%: ITT analysis) also, the median duration of response (38.1 weeks vs. 6.7 months) and the median progression-free survival (17.4 weeks vs. 4.6 months) respectively.
- Freyer and colleagues [13] reported that response rates tended to be higher in patients who did not present with visceral involvement, and had less than three organs affected. Amadori and colleagues confirmed this in their study, when they reported that the response rate was lower in patients with stage IIIb or IV disease at diagnosis, short disease-free interval, visceral involvement and/or three or more organs involved [14]. In both studies those patients who had received no prior adjuvant therapy showed the least response [13,14].
- The main reason for discontinuation in both trials was disease progression.
- Both of the studies were non comparative trials. Although Freyer and colleagues [13] compare oral and intravenous vinorelbine in their discussion, it is only a qualitative and not quantitative comparison. Randomised studies comparing intravenous with oral vinorelbine are needed to confirm equivalent efficacy and safety profiles.

6.1.3 Phase II trial of oral vinorelbine for the treatment of metastatic breast cancer in patients 65 years of age or older [16]

This was an open label, multicentre, phase II trial conducted to assess tumour response rate and the toxicity profile of oral vinorelbine as a single agent for first or second line chemotherapy in women at least 65 years old with metastatic breast cancer.

Eligible patients had histologically or cytologically confirmed stage IV breast cancer and had received at most one prior chemotherapy regimen for their metastatic disease. A total of 25 patients were enrolled with a median age of 73 years (range: 65-84 years). Of the 16 patients who had previously been treated for their metastatic disease, six (24%) had hormonal therapy, four (16%) had chemotherapy and six (24%) had both. Of the ten women who had received chemotherapy, six of them had been treated with anthracycline and/or taxane combinations. Within the whole study population, the majority of patients (72%) had dominant visceral metastases and most participants had positive oestrogen receptor status.

Oral vinorelbine was given as 60mg/m^2 BSA weekly for the first four doses and then increased to 70mg/m^2 BSA for subsequent administrations if there was no grade IV, or no more than one episode of grade III neutropenia. Therapy was continued until progression or intolerable toxicity occurred.

Results:

The median number of cycles administered was four (range: 1 to 20 cycles). All patients eventually discontinued treatment. Reasons for discontinuation included

progression of disease (18 patients: 72%), refusal to continue treatment (four patients: 16%), medical problems (two patients: 8%) and physicians' discretion (one patient: 4%). All but two patients began a second cycle of treatment. However, five of these patients did so at a reduced dose of at least 25% due to toxicities. Twelve of the remaining 18 patients received the increased dose of 70mg/m^2 BSA, however three patients required dose reductions to 60mg/m^2 BSA. Of the remaining six patients who began the second cycle at 60mg/m^2 BSA, only four were able to maintain that dose throughout the cycle.

All 25 patients were evaluated for tumour response. One patient (4%; 95%CI: 0.1% to 20.4%) achieved a partial response that lasted more than 13 months. Two additional patients remained stable (progression free) for 6.3 months and 11.5 months.

Points to note from the study:

- Unlike CA201 and CA206, patients in this study were evaluated for efficacy if they had received even one dose of oral vinorelbine. Complete or partial response was confirmed by two consecutive evaluations (using the RECIST criteria) [26,27] at an interval of six weeks apart rather than four weeks as in the previous studies.
- Interim analysis found that none of the first 12 patients enrolled had changes in their disease that met the RECIST criteria of a partial or complete response and as such the trial was closed to further accrual.
- Although relatively well tolerated, oral vinorelbine in this study was found to have little anti-tumour activity. Compared to the previous two trials (CA201 and CA206) the response rate in this study was significantly lower (30% and 26.4% vs. 4%, respectively).
- Of the patients remaining in this trial at the end of the second cycle, 60.8% (14 out of 23) were receiving a dose of 60mg/m^2 BSA or less. Therefore, the dose intensity administered was lower than in the previous studies. The company comment in their submission [12] that the median number of administrations was less in comparison to their studies [13,14], but Baweja and colleagues are reporting in terms of cycles not doses.
- In this trial patients were older than patients in the CA201 and CA206 trials (median: 73 years vs. 63 years) and were more likely to have metastatic disease with visceral involvement.
- Baweja and colleagues comment in their discussion that the patients in the Freyer trial [13] were less likely to have three or more metastatic sites (34% vs. 44%) [16].
- Sixteen (64%) patients had received at least one prior course of therapy for metastatic disease, 10 (40%) had received more than one regimen. Six patients had received prior chemotherapy that had involved anthracyclines and/or taxanes.
- In general, the participants in this trial would appear to be more applicable with regards to prior anthracycline based regimes, though patient numbers are low.
- Further studies investigating dose adjustment aimed at optimising the haematological tolerance of the patient while maintaining good tumour response are needed. A Phase II trial to define the biologically optimal dose of oral vinorelbine when administered at a metronomic schedule is currently underway in adults with recurrent or metastatic solid tumours including those with breast cancer [28].

6.1.4 Oral vinorelbine alone or in combination with trastuzumab in advanced breast cancer [12,17]

This pilot trial evaluated the efficacy and toxicity of oral vinorelbine in patients with advanced breast cancer as first line therapy or after progressing under earlier line chemotherapies alone or in combination with trastuzumab.

A total 78 patients, median age 63.5 years (range: 38-84 years), were included. According to their HER2 status, patients received either monotherapy with oral vinorelbine or a combination of oral vinorelbine and trastuzumab. Consequently, 57 patients received oral vinorelbine as monotherapy and 21 were in the combination-therapy group. Fifty percent (39) of the participants were receiving oral vinorelbine as first-line treatment, 33% (26) as second line therapy. Oral vinorelbine was used as third line in ten patients (12.8%), fourth line in two patients (2.6%), and fifth line in one patient (1.3%). No details were given regarding the prior chemotherapy regimens.

Vinorelbine was given orally at a dose of 60mg/m^2 BSA on day one and day eight in three week cycles without dose escalation. The combination therapy consisted of the same oral vinorelbine dose and trastuzumab, administered in a dose of 8mg/kg body weight loading dose on the first day and then followed by 6mg/kg body weight every three weeks. Re-evaluation of tumour status was every three cycles of therapy according to WHO criteria.

Efficacy Results:

For those receiving vinorelbine monotherapy and who were evaluable for efficacy (51 out of 57 patients), a PR was reported in ten patients (19.6%). Stable disease for greater than six months was reported in a further third (33.3%; 17 patients), resulting in a clinical benefit rate of 52.9%. Stable disease of less than six months but greater than three months was reported in two (3.9%), and progression of disease was found in the remaining 22 patients (43.1%) in this group.

For the combination group (17 out of 21 patients), four (23.5%) demonstrated a CR, five (29.4%), a PR; stable disease (greater than six months) was reported in six patients (35.3%), and PD in two (11.8%). The overall response rate was 52.9% with a clinical benefit rate of 88.2% recorded.

Points to note from the study:

- Although the tumour response evaluation criteria were similar to the studies carried out by the company (CA201 and CA206), CR was defined in this case as the disappearance of all measurable lesions for a minimum of eight weeks, not four.
- Data from 68 out of 78 participants were evaluated for efficacy. The reason why information was unavailable for some of the other participants was not made clear in the study.
- Response rates were much greater (overall: 52.9% vs. 19.6%) for the vinorelbine plus trastuzumab group though the number of patients was low.
- There was no complete response recorded for those receiving vinorelbine monotherapy.
- Bartsch and colleagues question whether a high overall response rate is more important than a high clinical benefit rate in metastatic patients.
- Randomised, prospective trials in a larger study population are needed to further assess the role of oral vinorelbine/trastuzumab in patients with HER2 positive advanced breast cancer.

- Further studies investigating the value of oral vinorelbine in combination therapy in general are also required.

6.1.5 Vinorelbine alternating oral and intravenous plus epirubicin in first-line therapy of metastatic breast cancer: results of a multicentre phase II study [12,18]

This open label, multicentre phase II study alternated intravenous and oral vinorelbine in combination with epirubicin as first line therapy for patients with metastatic breast cancer. All 49 patients received intravenous vinorelbine 25mg/m^2 BSA plus epirubicin 90mg/m^2 BSA given on day one and oral vinorelbine 60mg/m^2 BSA on day eight (or day 15 if neutrophils were less than 1500/mm^3) every three weeks. The study population were relatively young with a median age of 55 years, and over half (57%, 28 out of 49 patients) had received prior adjuvant chemotherapy containing an anthracycline or anthracenedione. The majority (86%) also presented with visceral involvement.

In the intention to treat analysis twenty five patients had a response, yielding a response rate of 51% (95% CI: 36 to 66%). The proportion of responders was similar in patients who had received prior anthracycline/anthracenedione containing adjuvant chemotherapy (50%; 8 out of 16 patients) and those who had not (52%; 17 out of 33 patients). The median durations of progression free survival and survival were eight and 20 months, respectively.

6.1.6 Combination studies (presented in abstract form) [19,20]

Two phase I/II studies combining capecitabine with oral vinorelbine as first, second, or subsequent line chemotherapy in patients with locally advanced or metastatic breast cancer were also highlighted in the company submission. In the study by Gligorov and colleagues [19] 13 out of the 16 participants had received adjuvant anthracycline treatment, but no information was available on this in the other study by Delcambre and colleagues [20]. In both studies the all oral combination appeared to be active and reasonably well tolerated, however further details would be necessary to confirm the results.

6.2 Safety:

Neutropenia was the main haematological toxicity of oral vinorelbine reported during clinical trials (especially where treatments were initiated at 80mg/m^2 BSA) and led to the development of severe neutropenic complications in some patients. Therefore, if patients present signs or symptoms suggestive of infection, a prompt investigation is warranted[1]. In clinical trials haematological toxicity was the principal reason for dose delay and modification.

Overall rates of neutropenia and grade III or IV neutropenia were higher during administrations at 80mg/m^2. Notably, in their discussion, Bartsch and colleagues consider that a gain in overall response rate (using a higher dose than 60mg/m^2 BSA in their case) would be outweighed by the resulting increase in toxicity. Usually, severe toxicities happened within the first three administrations.

Non haematological toxicities most frequently reported from clinical studies were nausea and vomiting (no primary prophylaxis with anti emetics was mandated in any of the studies). Anti-emetics may reduce the occurrence of this[1]. Gastrointestinal events reported with grade III-IV severity were nausea, vomiting, diarrhoea and anorexia. Neuro-constipation was observed in some patients but not considered severe. Other common undesirable effects in the SPC included; neurosensory disorders, alopecia, fatigue, arthralgia, and transient elevation of liver function tests (without clinical symptoms) [1]. Concerns over an increased incidence in neuropathy

with vinorelbine in patients with taxane refractory tumours should be clarified by the present RCT being undertaken by the EORTC [30].

Although oral vinorelbine would appear to be relatively well tolerated for the majority of the trial population, the treatment is used as first line therapy. As such, patients may have been less haematologically vulnerable than those who would have previously received chemotherapy for advanced breast cancer.

There have been rare reports of angina and myocardial infarction with vinorelbine IV; special care is therefore advised when prescribing for patients with a history of ischaemic cardiac disease[1]. Cardiac dysrhythmia has very rarely been reported.

As CYP 3A4 is mainly involved in the metabolism of vinorelbine, combination with inducers or inhibitors of this isoenzyme may alter the pharmacokinetics of vinorelbine. Omeprazole and fluoxetine (norfluoxetine), inhibitors of CYP3A4, were both found to moderately inhibit the metabolism of vinorelbine, although the clinical relevance of this inhibition is unknown. When combined with anti emetics (metoclopramide or $5HT_3$ antagonists) the vinorelbine pharmacokinetics is not modified[1].

The combination of oral vinorelbine with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects. Further details on special warnings and precautions can be found in the Summary of Product Characteristics[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

7.1.1 Chemotherapy:

In patients who have not been previously exposed to anthracyclines in the adjuvant setting, a first line treatment option for metastatic disease consists of an anthracycline-containing combination such as doxorubicin or epirubicin plus cyclophosphamide or cyclophosphamide and 5-fluorouracil, plus doxorubicin or epirubicin [5]. The clinical usefulness of these agents, however, can be limited by their toxicity profiles, which include events such as myelosuppression, acute nausea and vomiting and alopecia. Cardiomyopathy is related to cumulative dose and a maximum total cumulative dose for both epirubicin and doxorubicin has been recommended to help avoid cardiotoxicity[31].

The taxanes, docetaxel and paclitaxel, have an established role as a second line treatment in metastatic breast cancer, especially in people with disease progression despite a previous anthracycline based regimen [2,5]. Nevertheless, taxane based chemotherapy has been found to be associated with more neurotoxicity and alopecia than non taxane based regimens [2].

The oral fluoropyrimidine capecitabine has been reported as achieving a response rate of 15 to 26 per cent and median survival of approximately one year in patients with metastatic breast cancer that has progressed during or following anthracycline and taxane therapy [2,5]. Capecitabine has a low incidence of myelosuppression making it highly suitable for combination therapy[32]. Accordingly, several studies have been carried out including a phase III RCT with docetaxel and other studies involving oral vinorelbine, which have shown encouraging results [32-35]. Furthermore, the European Organisation for Research and Treatment of Cancer (EORTC) is currently comparing oral capecitabine to intravenous vinorelbine in a phase II/III randomised trial performed in a population of patients pre-treated with anthracyclines and taxanes

[30]. However, given the lack of randomised trials, the place of capecitabine in the treatment of advanced breast cancer is yet to be determined [36].

7.1.2 Hormonotherapy:

Trastuzumab is used in the treatment of metastatic breast cancer for patients with tumours overexpressing the human epidermal growth factor receptor 2 (HER2) and produces significant antitumour activity in such patients, either alone [37] or in combination with chemotherapy [38].

7.2 Comparative effectiveness:

- Pharmacokinetic studies in non small cell lung cancer patients have shown bioequivalence between the oral and intravenous preparations of vinorelbine [39], but at this time there are no published efficacy and safety data that directly compares oral vinorelbine to intravenous vinorelbine, although qualitatively they appear to be similar.
- A small number of Phase I or II combination studies, involving oral vinorelbine, have shown encouraging results [33-35].
- From the studies available vinorelbine is clearly an active agent in the treatment of advanced breast cancer and has a relatively milder toxicity profile over some other more established cytotoxic agents.
- An advantage of this treatment over some other current therapies is that oral vinorelbine offers a more convenient method of administration and can be taken at home.
- There is, however, a lack of randomised controlled trials and comparative data. In particular, more studies carried out in the context of those relapsing after or refractory to an anthracycline containing regimen are needed in order to clarify the role of oral vinorelbine both as a single agent and in combination therapy in the treatment of advanced breast cancer.
- Further well-designed prospective studies are needed in order to provide more information on safety, tolerability and the optimal dose especially in patients with pre-treated metastatic breast cancer and should include randomised studies comparing IV with oral vinorelbine to confirm equivalent efficacy and safety profiles.
- Further studies investigating the value of oral vinorelbine in comparative clinical trials (including taxanes) would also help clarify the place of oral vinorelbine in the management of advanced breast cancer.
- The European Organisation for Research and Treatment of Cancer (EORTC) is currently comparing intravenous vinorelbine to oral capecitabine to in a phase II/III randomised trial performed in a population of patients pre-treated with anthracyclines and taxanes [30].
- In the studies submitted oral vinorelbine was mostly used as a first line therapy in advanced disease and the majority of patients had not received prior anthracycline based chemotherapy. This does not fit with the current NICE guidance where vinorelbine (IV) monotherapy is recommended as one option for second line or later therapy for the treatment of advanced breast cancer when anthracycline-based regimens have failed or are unsuitable.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of key economic issues:

The key economic questions for AWMSG to consider are:

1. Whether the potential additional benefits offered by an oral formulation of vinorelbine, compared to vinorelbine (IV), justify any differences in the costs and

2. Whether the budgetary impact of introducing an oral formulation of vinorelbine is acceptable.

8.2 Review of published evidence on cost effectiveness:
There are no specific studies that have assessed the cost-effectiveness of vinorelbine (oral). However, the cost effectiveness of vinorelbine (IV) has been assessed in relation to the treatment of patients with advanced breast cancer and non-small cell lung cancer.

In a systematic review of the clinical and cost effectiveness of vinorelbine in the management of breast cancer, four economic evaluations were included [40].Three examined vinorelbine, docetaxel and paclitaxel and one compared capecitabine, vinorelbine, 5-fluorouracil and gemcitabine. The three economic evaluations of vinorelbine, docetaxel and paclitaxel were of reasonable quality but, for the fourth, there was limited information because it was only available as an abstract.

One Canadian evaluation[41], comparing vinorelbine, docetaxel and paclitaxel, found vinorelbine to be more effective and less costly than paclitaxel and docetaxel, with a cost per quality-adjusted progression-free year of Can$31,220 (£14,588) for vinorelbine, Can$59,096 (£27,615) for paclitaxel and Can$110,072 (£51,436) for docetaxel. A UK study, sponsored by the manufacturer of docetaxel, found vinorelbine to be less effective and less expensive than both docetaxel and paclitaxel[42]. The third economic evaluation (based in France) found that vinorelbine, when compared to docetaxel, was found to have a higher cost and poorer outcomes [43].

When generalising these data to the UK, vinorelbine is usually considered as an alternative to taxane therapy for patients who cannot tolerate intensive treatment, rather than as a replacement for it.

Similarly, in a systematic review of the clinical and cost effectiveness of vinorelbine and other treatment options in non-small cell lung cancer, it was concluded: “although the clinical benefits of the new drugs appear relatively small, their benefit to patients with lung cancer appears to be worthwhile and cost effective”[44].

8.3 Review of company submission on cost-effectiveness:
8.3.1 Summary of the evidence:
The company submission reports on a cost-minimisation model which compares the costs associated with vinorelbine (oral) and vinorelbine (IV) from the perspective of the NHS in Wales. It demonstrates that overall cost savings from switching from the IV to oral formulation of vinorelbine are made, ranging from £800 to £2630 per patient, depending on treatment regimen and resulting mainly from savings on hospital resource usage and transportation. The choice of such an approach meant that no cost per QALY data was included in the submission.

8.3.2 Summary of the key findings
There are some concerns over the use of cost-minimisation analysis especially given the lack of a direct comparison and differences in the adverse event profiles. However, the model does take into consideration the potential additional resource implications resulting from the use of anti-emetics and uses an expensive treatment to demonstrate the overall cost difference between the two routes of administration.

From the patients’ perspective there are obvious advantages of an oral formulation, which might be offset by the increased incidence of adverse events, but on the

assumption that the oral formulation is similar to the IV regimen, then it is reasonable to assume that the oral formulation of vinorelbine would be cost effective relative to IV vinorelbine.

8.4 Review of evidence on budget impact:

8.4.1 Summary of the evidence:

The budget impact discussion follows closely from the cost-minimisation analysis. In their submission, the company estimate 1000 patients per year will present or relapse with advanced breast cancer in Wales [12]. Currently in Wales around 75 women with advanced breast cancer receive IV vinorelbine per year [12]. Based on experience in Europe, the company predict that the majority of patients would be converted from IV to oral vinorelbine. This would generate annual savings of between £92,000 and £131,000, mainly in hospital resource usage and costs associated with transportation. Whether or not other patients would be eligible for oral vinorelbine is not considered.

8.4.2 Summary of the key findings:

The impact of switching patients to oral vinorelbine from IV vinorelbine in Wales would generate annual savings of between £92,000 and £131,000, mainly in hospital resource usage and costs associated with transportation.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- A review of the safety data from earlier trials showed an excessive rate of early deaths due to complicated neutropenia (10% of the overall study population) when initially using 80mg/m^2 BSA [29]. The SPC highly recommends that the appropriate dosing schedule should be followed[1].
- Dose reduction from 80 to 60mg/m^2 BSA as a result of hematological toxicity may be needed. It may be possible to re-escalate the dose to 80mg/m^2 BSA if no further toxicity is reported.
- Close haematological monitoring should be undertaken during treatment (i.e. determination of haemoglobin level, leucocyte, neutrophil and platelet counts on the day of each new administration) [1].
- Food has been found to have no influence on absorption or pharmacokinetics, but the incidence of vomiting appeared to be lower in fed patients versus fasted patients in a small study by Bugat and colleagues [45].
- If treatment is supported within NHS Wales, a physician experienced in the use of chemotherapy should prescribe oral vinorelbine.
- It is the view of AWMSG that, oral vinorelbine is currently not deemed suitable for shared care.

9.2 Related advice:

The Scottish Intercollegiate Guidelines Network (SIGN) published guidelines on the management of breast cancer in women in 2005 [36].

9.3 Previous AWMSG/NICE advice

National Institute for Health and Clinical Effectiveness (NICE) has commissioned the National Collaborating Centre for Cancer to develop a clinical guideline on the diagnosis and treatment of metastatic breast cancer[52] In February 2005, the Institute consulted on the proposal that its guidance on vinorelbine for the treatment of advanced breast cancer (TAG no.54) [10], its guidance on capecitabine for the treatment of locally advanced or metastatic breast cancer (TAG no.62) [4] and its

guidance on trastuzumab for advanced breast cancer (TAG no.34) [3] and the use of taxanes[46] should all be updated and incorporated into the new guideline. Current guidance will remain in place until the new guideline is published, which is not expected until January 2009.

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Appendix 1. Additional clinical information

There is nothing to add.

Appendix 2. Health Economic Review

1 The research question is stated

Yes the submission makes this explicit.

2 The economic importance of the research question is stated

Yes, and the context relating to chemotherapy services is discussed.

3 The viewpoint(s) of the analysis are clearly stated and justified

Yes, the NHS in Wales and with consideration given to patient issues such as transportation costs.

4 The rationale for choosing the alternative programmes or interventions compared is stated

The company consider that Navelbine® is a line extension to the existing intravenous formulation, and that based on experience elsewhere the major impact has been a switch from use of the IV formulation, in both non-small cell lung cancer and advanced breast cancer indications, rather than replacing other therapeutic agents. Thus the comparison is between the oral and IV formulations.

5 The alternatives being compared are clearly described

Yes.

6 The form of economic evaluation used is stated

Yes a cost-minimisation analysis is undertaken.

7 The choice of form of economic evaluation is justified in relation to the questions addressed

While the submission assumes that there is no difference in effectiveness between the oral and IV formulations and would thus be appropriate to justify a cost-minimisation analysis, no direct evidence is provided to support this. Furthermore, evidence is presented of differences in adverse events between the oral and IV formulations, which would mean that the outcomes from the formulations could not be said to be equivalent – the fundamental requirement for cost-minimisation analysis[47].

8 The source(s) of effectiveness estimates used are stated

Yes - two Phase II studies of oral vinorelbine in advanced breast cancer [13,14] and one study of IV vinorelbine in advanced breast cancer [7] but there are no comparative studies comparing routes of administration.

9 Details of the design and results of effectiveness study are given (if based on a single study)

Not available.

10 Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)

A series of indirect comparisons are made between the studies which demonstrate that the outcomes obtained with oral vinorelbine are within the same range as those for the intravenous formulation of vinorelbine, in terms of median duration of response, progression free survival and median survival.

However, this does not necessarily meet the criteria for conducting a cost-minimisation analysis.

11 The primary outcome measure(s) for the economic evaluation are clearly stated
In a cost-minimisation analysis the primary outcome measure is that of cost.

12 Methods to value health states and other benefits are stated
Not available.

13 Details of the subjects from whom valuations were obtained are given
Not available.

14 Productivity changes (if included) are reported separately
Not included in analysis but recognised as a potential additional benefit resulting from oral formulation.

15 The relevance of productivity changes to the study question is discussed
Not available.

16 Quantities of resources are reported separately from their unit costs
Yes – and a series of clinical scenarios are presented.

17 Methods for the estimation of quantities and unit costs are described
Yes – based on discussions with oncologists in UK, relevant Phase II trial data, routine clinical practice and published sources.

18 Currency and price data are recorded
Yes – prices converted to UK 2006 prices using appropriate indices.

19 Details of currency of price adjustments for inflation or currency conversion are given
Data from published sources updated using purchasing power parity index.

20 Details of any model used are given
A spreadsheet model was made available by the manufacturer.

21 The choice of model used and the key parameters on which it is based are justified
The choice of cost-minimisation is questionable. The evidence for equivalent outcomes from different routes of administration is lacking. In addition, there are different adverse event profiles associated with the different routes of administration, and while the probable resource implications of treating these were included in the model, no attempt was made to assess the utility impact of the higher reported incidences of nausea and vomiting.

Analysis and interpretation of results:

22 Time horizon of costs and benefits is stated
The time horizon was based on four cycles of chemotherapy – based on relevant clinical trials – and was less than twelve months.

23The discount rate(s) is stated
Not applicable.

24 The choice of rate(s) is justified
Not applicable.

25 An explanation is given if costs or benefits are not discounted
Time horizon is less than twelve months.

26 Details of statistical tests and confidence intervals are given for stochastic data
No.

27 The approach to sensitivity analysis is given
A series of one-way sensitivity analyses were undertaken based on differences in dosing schedules.

28 The choice of variables for sensitivity analysis is justified
Yes – determined by discussion with clinicians.

29 The ranges over which the variables are varied are stated
Yes.

30 Relevant alternatives are compared
No.

31 Incremental analysis is reported
Savings between formulations per patient are the primary measure of outcome.

32 Major outcomes are presented in a disaggregated as well as aggregated form
Yes – it is possible to determine where the savings and additional costs occur.

33 The answer to the study question is given
Yes.

34 Conclusions follow from the data reported
Yes.

35 Conclusions are accompanied by the appropriate caveats
The submission considers the cost differentials between modes of administration when differing dosing schedules and different costs for patient transportation were used.

Appendix 3. Summary of Medical Expert Opinion

- Velindre Hospital management policy and NICE Guidance are followed.
- Breast cancer is relatively chemo-sensitive, and it is common to use single agents in sequential order.
- The usual regime would be to use an anthracycline followed by taxanes or capecitabine for the less fit. Intravenous vinorelbine is used after failure of these.
- A total of 30 to 40 patients at Velindre Hospital would be eligible annually.

Appendix 4. Patient Interest Group submissions (provided as a separate document)

Appendix 5. Company written response (provided as a separate document)