National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG108 Vinorelbine | Advice Document v1.0 | April 2023

Vinorelbine as a second- or subsequent-line treatment of adult patients with malignant pleural mesothelioma whose disease has progressed on or after platinum-based chemotherapy, with or without prior immunotherapy

NCMAG Decision | This off-label use of vinorelbine is **not supported**

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

Decision rationale

Following careful review of the clinical evidence, the council deemed that the clinical benefit-risk balance was uncertain and was insufficient to support use in the full proposed patient population.

Proposal Details	
Proposers	Clinicians treating mesothelioma tumour groups from across NHSScotland regional cancer networks
Medicine Name	Vinorelbine
Cancer type	Malignant pleural mesothelioma
Proposed off-label[B]	As a second- or subsequent-line treatment of patients with malignant pleural mesothelioma whose disease has progressed on or after platinum-based chemotherapy, with or without immunotherapy
Medicine Details	Form: Capsule Dose: 60mg/m^2 of body surface area orally on day 1, 8 and 15 of a 21-day cycle, increasing to 80mg/m^2 from cycle 2 onwards if tolerated. Treatment should continue until evidence of disease progression or unacceptable toxicity.[1]

[B] Vinorelbine has a marketing authorisation as a single agent or in combination for:

- The first line treatment of stage 3 or 4 non small cell lung cancer.
- The treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.[2]

1. Current Management Context

Malignant mesothelioma incidence, symptoms and prognosis

Malignant mesothelioma is a type of cancer that primarily originates in the pleura and peritoneum but can also affect the heart and testes. It is associated with asbestos exposure which causes chronic inflammation and DNA damage resulting in cancer. The mean age at the time of diagnosis for malignant pleural mesothelioma (MPM) is approximately 76 years in the UK. Most cases occur in males (83%), with the majority related to occupational asbestos exposure.[3] In 2017, there were 194 mesothelioma diagnoses in Scotland, and approximately 50 patients per year received first-line systemic anti-cancer therapy.[4]

Symptoms of pleural mesothelioma include breathlessness, haemoptysis, chest pain, fatigue, cough and weight loss. The benefit of surgery in pleural mesothelioma is uncertain.

MPM has a very poor prognosis. In England and Wales survival rates after diagnosis of MPM at one year and three years are 40% and 10%, respectively. Of the three main histological subtypes of MPM (epithelioid, sarcomatoid, and biphasic), the epithelioid subtype is generally associated with the best prognosis.[3]

International context for the proposed off-label use

There is no standard second and subsequent-line treatment options for MPM. Both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) support the use of cisplatin or carboplatin and pemetrexed as second-line options if immunotherapy was used first-line. Re-challenge with chemotherapy is an option if patients had a good sustained response with chemotherapy in the first-line setting. These guidelines mention use of off-label gemcitabine or vinorelbine as possible options in the second line setting.

Pharmacology of vinorelbine

Vinorelbine is an orally active vinca alkaloid that prevents mitosis by inhibiting functional microtubulin formation: this results in cancer cell death.[2] Main side effects include reduced white cell count, anaemia, low platelets, fatigue, diarrhoea and constipation.[2]

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including Medline and Embase. The main search concepts were vinorelbine and mesothelioma. No filters were applied to limit the retrieval by study type. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key research study was critically appraised using the Cochrane risk of bias version 2.0 tool.

Healthcare Improvement Scotland

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

Evidence comparing vinorelbine versus active supportive care

The key evidence source relevant to the proposal of using vinorelbine in patients with progressed malignant pleural mesothelioma (MPM) is the Vinorelbine in Mesothelioma (VIM) study.[1] The VIM study was a phase ll open label, multicentre, randomised controlled trial, which compared active symptom control (ASC; supportive care for pain management) plus oral vinorelbine with ASC alone in patients with MPM who had radiological evidence of disease progression after at least one course of platinum-based chemotherapy. Maintenance treatment (delivered within a clinical trial) following first-line treatment was permitted as was re-challenge therapy with a first line platinum doublet. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, a life expectancy of ≥3 months and measurable disease according to modified Response Evaluation Criteria in Solid Tumors (RECIST) or RECIST version 1.1 were included. In the study, 154 patients were randomly assigned (2:1) to receive either ASC plus vinorelbine (n=98) or ASC (n=56). Minimisation factors included best response to first-line therapy, histology, gender, white cell count and ECOG performance status. The primary outcome was progression-free survival (PFS), defined as the time from randomisation to disease progression or death, whichever occurred first. Secondary outcomes included the following - overall survival (defined as the time from randomisation to death of any cause), overall response to treatment using the modified RECIST and safety. Patients were followed up until disease progression, complete withdrawal or death and for 6 months after completion of recruitment.

Results from the Vinorelbine in Mesothelioma (VIM) study

The median age of patients was 71 years with the majority being male (81%), having an epithelioid subtype (84%) and a best response during first line therapy of 'complete or partial response, or stable disease' (73%). The ECOG performance score was 0 in 25% of patients and 1 in 75% of patients. Investigator-assessed PFS improved with the use of ASC plus vinorelbine compared with ASC only with no difference in median overall survival between groups (See Table 1).

Table 1 | Results for primary and secondary outcomes[1, 7]

	ASC plus vinorelbine (n=98)	ASC (n=56)
Primary outcome: PFS assessed by investigator per modified RECIST		
PFS events, %	82 (84)	47 (84)
Median PFS, months (IQR)	4.2 (2.2-8.0)	2.8 (1.4-4.1)
Adjusted hazard ratio (80%CI one-sided, upper value)	0.60 (0.7)	
Secondary outcome: overall survival		
Overall deaths[a,b], %	70 (71)	38 (68)
Median overall survival, months (95%CI)	9.3 (6.7-11.9)[a]	9.1 (5.7-14.2)[a]
Unadjusted hazard ratio (95%CI)	0.79 (0.53-1.17)[a]	
Secondary outcome: objective response rate per modified RECIST[c]		
Partial response, n(%)	3 (3)	1 (2)
Median duration of response overall, months (IQR)	7.2 (3.1-8.5)	4.2 (4.2-4.2)

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[a]Unpublished supplementary table/personal communication
[b]Cause of death in the ASC plus vinorelbine group and ASC group - disease progression: 59 (60%) and 29 (52%); treatment-related toxicity; 1 (1.0%) and 0; other: 4 (4.1%) and 4 (7.1%); missing: 6 (6.1%) and 5 (8.9%), respectively.
[c]Number missing in the ASC plus vinorelbine group and ASC group was 6 (11%) and 7 (13%), respectively.
Number who did not reach Cycle 2 RECIST assessment in the ASC plus vinorelbine group and ASC group was 7 (7%) and 8 (8%), respectively.
PFS: progression-free survival; IQR: interquartile range; CI; confidence interval; NR: not reached.

Other evidence sources

Three non-comparative studies were identified which had the aim to evaluate the efficacy of vinorelbine in patients with MPM.[8-10] Two were consecutive cohort studies (one retrospective and one prospective)[8, 10] and one study was a phase II single-arm trial.[9] The number of patients included ranged from 15 to 63 and the majority of patients included in each of the studies were administered vinorelbine as a second line therapy. An overview of the results of these studies are in Table 2.

Table 2 | Summary of non-comparative studies and results[8-10]

Study name, year Country (design)	Patients at 2nd line n (%)	Follow-up (months)	Objective response rate[a] n (%)	Median PFS, months (range)	Median overall survival months (95%CI)
Sørensen 2012, Denmark (PC)	15 (100)	Not reported	1 (7)	2.5 (range: 0.4 to 10.3)	4.5 (range: 4.5 to 23)
Stebbing 2009, UK (phase II trial)	63 (100)	Not reported	10 (16)	Not reported	9.6 (7.3 to 11.8)
Zucali 2014, Italy (RC)	34/59 (58)	18.1 (0.8 to 27.8)	5 (15)	2.3 (range: 0.6 to 22.5)	6.2 (range: 0.8 to 27.8)

[a]Response to treatment was evaluated according to the modified RECIST criteria.
PC: prospective cohort; RC: retrospective cohort

Patient-reported outcomes

Patient-reported outcomes including quality of life were not evaluated in any of the studies.

Safety evidence

Based on data from the VIM study, the most frequently reported treatment-related adverse events of any grade in the ASC plus vinorelbine group versus the ASC only group were fatigue (52% versus 22%), constipation (40% versus 8%), dyspnoea (32% versus 18%), diarrhoea (25% versus 4%), anaemia (24% versus 10%). The most frequently reported grade 3 or above adverse events in the ASC plus vinorelbine group compared to the ASC group were neutropenia (13% versus 0%), dyspnoea (6% versus 0%) and lower respiratory infection (5% versus 6%). The most common cause of SAEs in the ASC plus vinorelbine group versus the ASC only group were: dyspnoea (5% versus 0%), lower respiratory tract infection (5% versus 6%), unspecified infection (3% versus 0%) and febrile neutropenia (3% versus 0%). Two respiratory treatment-related deaths were reported in the vinorelbine plus ASC group. In the vinorelbine plus ASC group, missed doses and dose interruptions (at least one dose reduction) was reported in 35% of patients with nearly 50% of patients having at least one dose delay. Within the limits of interpreting small patient numbers,

the safety profile of vinorelbine in the VIM study is consistent with the on-label indications for vinorelbine.[2]

Quality assessment of clinical evidence

Although considered to have appropriate design features for a phase II study, there were a few areas of concern in relation to risk of bias that were identified on appraisal of the VIM study. The randomisation process was conducted centrally, however, the details of treatment allocation were not reported. Progression-free survival was investigator-assessed and not centrally reviewed; given the open-label design and recognised challenges of assessing this outcome in mesothelioma this does pose some concern. Participant choice as a reason for withdrawal was higher in the ASC group than in the vinorelbine plus ASC group which could be explained by a difference in health-related behaviours as a consequence to awareness of group allocation. Due to the phase II screening design of the VIM study the risk of a false positive result for PFS was set higher than routinely seen in phase III studies. An explanation is provided in the protocol (unpublished) that the original primary outcome, overall survival, was changed to PFS during the study due to the high numbers of patients either crossing over to vinorelbine or taking up other treatments. The risk of bias that this would pose on the overall survival outcome underpins the VIM trial steering committee's decision to change the primary outcome to PFS. Please note the online appendix as referred to in the published results paper was not available at the time of writing this advice document. The study team, on request, provided the study protocol and supplementary data tables.

Clinical effectiveness considerations

There was a modest improvement in progression-free survival

In the vinorelbine plus ASC arm, 60% of patients (59 out of 98) progressed. In the ASC arm, 62% of patients (35 out of 56) progressed. The progression-free survival was 4.2 months (interquartile range [IQR] 2.2 to 8.0) in the vinorelbine plus ASC group and 2.8 months (IQR 1.4 to 4.1 months) in the ASC group.

The open-label and investigator assessed study design may have confounded results for PFS and overall survival.

It is recognised that objective assessment of response in MPM is challenging.[11] Furthermore, the VIM study was open-label and CT scans were not centrally assessed. CT scans were conducted every 6 weeks (or 1.2 months), which could make this the minimum impact in the presence of detection bias.

It is unclear what impact awareness of other concurrent trials may have had on detection and withdrawal from the open-label VIM trial. In the ASC arm, 52% of patients received subsequent treatment (40% entered clinical trials and 12% received other SACT), while in the vinorelbine plus ASC arm, only 6% of patients received subsequent line therapy. Taken together it increases the uncertainty of the modest improvement in investigator-assessed PFS of 1.4 months and it is unclear if this is a clinically significant difference.

Overall survival was originally the primary study outcome, however it was changed to a secondary outcome in a protocol amendment. Median overall survival did not differ significantly between arms. Treatment crossover and an imbalance in subsequent lines of therapy across treatment arms may have a confounding effect on overall survival data.

Evidence for vinorelbine after treatment with immunotherapy is limited

The current treatment pathway for MPM has evolved since the VIM study. First-line treatment now includes doublet immunotherapy with nivolumab and ipilimumab, and fit patients are likely to now receive cisplatin and pemetrexed in the second-line setting. However, the patient population in the VIM study did not include patients who were treated with second-line cisplatin and pemetrexed after first-line immunotherapy. No supporting published studies were found that examined the efficacy of vinorelbine after immunotherapy.

Evidence for vinorelbine in the third-line setting is limited

It has been suggested that vinorelbine could be an option in the third line setting.[1] However, the VIM study did not provide detailed information on the efficacy and tolerability of vinorelbine in this context. Zucali et al conducted a retrospective, single-centre study in patients with malignant pleural mesothelioma (MPM) using intravenous vinorelbine at various dosing schedules.[10] The study found no differences in PFS or overall survival between the group that received vinorelbine in the second-line setting and the group that received it beyond the second line. Consistent with findings from the VIM study, responders to chemotherapy in the first-line setting were more likely to derive benefit from vinorelbine.[8] Overall, there is limited direct evidence on the efficacy of vinorelbine in the third-line setting.

VIM is likely generalisable to the Scottish population who have not previously been treated with immunotherapy

The VIM study was a UK based multi-centre trial. The VIM study reported a median age of 71 years, which is likely representative of Scottish practice. The Scottish Cancer Medicines Outcome Programme found that the median age of patients who receive first-line chemotherapy for MPM in Scotland is also 71 years old. The proposal eligibility criteria matches those of the VIM study, including performance status.

There is a lack of efficacious second and subsequent-line treatments for MPM

There is limited evidence of second line and beyond therapies providing overall survival benefit in MPM. A recent clinical trial showed that nivolumab with or without ipilimumab provided benefit in immunotherapy-naive patients. In contrast, pembrolizumab did not demonstrate PFS or overall survival benefit compared to vinorelbine or gemcitabine.[12] Targeted therapies have also failed to show superiority over vinorelbine in the second-line setting.[13]

The open-label study design may have confounded patient reported outcomes and safety

Grade 3 or higher neutropenia was reported for 13% of patients receiving vinorelbine plus ASC arm, compared to 0% for the ASC arm. Dyspnoea was reported for 6% of patients receiving

vinorelbine compared to 0% for the ASC arm. As patients and investigators knew patients were not on active treatment there may have been overestimation of treatment related side effects for constitutional symptoms like dyspnoea.

4. Patient group summary

Two patient group partner statements were received from Action on Asbestos and Mesothelioma UK. The key points are summarised below:

- Mesothelioma is a rare and aggressive cancer with a poor prognosis, and the median survival rate is reported to be between 8 and 12 months from diagnosis. Treatment and management options are extremely limited.
- The main cause of mesothelioma is occupational exposure to asbestos.
- The physical impact of living with mesothelioma can include significant fatigue, pain, breathlessness, and coughing. The psychosocial impact includes anxiety, grief, antagonism, and feelings of helplessness.
- Having more treatment options is a priority for the mesothelioma community, and given the longer progression-free survival for patients treated in the VIM study, the patient group partners fully support patients having access to this treatment.

In summary | Mesothelioma is a rare and aggressive cancer with a poor prognosis, caused by occupational exposure to asbestos. Having access to more treatment options would offer hope to patients.

5. Benefit-risk balance

Vinorelbine may offer a modest improvement in PFS in the second-line setting and beyond, compared with ASC, in a context of a lack of efficacious treatment options for MPM. However, there are important weaknesses in the supporting evidence that make the PFS data uncertain. Also there is uncertainty regarding the use of vinorelbine after immunotherapy or in the third line setting. The side effect profile of vinorelbine appears to be similar to its licensed indications, with grade 3 or higher neutropenia (reported for 13% of patients receiving vinorelbine versus 0% for the control arm) and dyspnoea (reported for 6% of patients receiving vinorelbine versus 0% for the control arm).

6. Council Review |Clinical benefit-risk balance evaluation

The Council deemed that the clinical benefit-risk balance was uncertain and was insufficient to support use in the full proposed patient population.

7. Economic Evidence Review Summary

Economic Overview

Type of economic evaluation

No relevant published cost-utility analysis was identified in the literature search. A cost-comparison was the primary analysis performed. Additionally, a simple exploratory cost-utility analysis forms part of the wider cost-effectiveness considerations.

Population, intervention, comparator and outcomes

The population was patients with malignant pleural mesothelioma whose disease has progressed on or following platinum doublet chemotherapy with or without separate prior immunotherapy. The intervention was oral vinorelbine. As there are no licensed medications in this population, there was no comparator treatment. As a cost-comparison was performed, quality-adjusted life-years (QALYS) were not required in the analysis.

Costs

Medicine acquisition and monitoring costs were considered. Vinorelbine was costed as 60mg/m^2 of body surface area with a 108mg dose (assuming 1.8m^2 BSA) on day 1, 8 and 15 of a 21-day cycle, increasing to 80mg/m^2 with a 144mg dose (assuming 1.8m^2 BSA) from cycle 2 onwards. Monitoring costs included clinic appointments, as well as CT scans. Costs were calculated for 2.8 months (4 cycles) of treatment, for consistency with the median duration of exposure in the VIM study.

Key results

The medicine acquisition cost of vinorelbine was estimated at £3,958 (BNF medicine list prices) per patient. Including monitoring costs, this figure was £4,296 (BNF medicine list prices) per patient.

Cost-effectiveness considerations

Generalisability of the cost-comparison

The dosing regimen of vinorelbine was from the VIM study and is the intended regimen in NHSScotland.

Results using NHSScotland national framework contract prices were considered in confidence.

Limitations of the cost comparison

Due to an absence of a published cost-utility analysis, the cost comparison only compares costs. Vinorelbine is a cost increasing intervention. However, as a published ICER is unavailable, the cost-effectiveness remains unknown.

There are no licensed medications in this population. In practice, active symptom control (ASC) may be offered but its impact on cost results is likely limited as clinical expert opinion supported that vinorelbine is given in addition to ASC.

Treatment related adverse events were not included in the cost comparison. This is a simplification. Given the increase in adverse events observed in the VIM study for vinorelbine plus ASC versus ASC alone, it can be expected that adverse events could potentially increase costs for vinorelbine.

Exploratory cost utility analysis

There were no published ICERs for vinorelbine in this population. However, an exploratory cost-utility analysis was performed to estimate an ICER based on key clinical outcome data and costs (Table 3). As there may be limited subsequent treatments, and a short treatment duration, a model with an extended time horizon is unlikely to be required and the analysis may provide a useful guiding insight on the ICER.

Table 3 | Summary of parameters used in ICER estimation

Parameter	Value	Justification	Source
OS Vinorelbine	9.3 months	Reported median OS	Fennell et al., 2022[1]
OS SOC (ASC)	9.1 months	Reported median OS	Fennell et al., 2022[1]
PFS Vinorelbine	4.2 months	Reported median PFS	Fennell et al., 2022[1]
PFS SOC (ASC)	2.8 months	Reported median PFS	Fennell et al., 2022[1]
Estimated utility value	0.62	Second line mesothelioma utility values are uncertain. Utility obtained from the "post-progression" health state for first line treatment in NICE TA818- Used as a proxy for patients starting this second line treatment	NICE TA818[14]
Estimated utility value (further progression)	0.506	The decrement observed in utility between "progression-free" and "post-progression" in NICE TA 818 was 0.732-0.62=0.114. This was considered as a proxy for the decrement in utility for further progression, hence 0.62-0.114=0.506.	NICE TA818[14]
Incremental treatment cost	£4,296	Calculated assuming 2.8 months (4 cycles) of treatment. Figures inclusive of monitoring. Dosing and resource use frequency consistent with the cost-comparison.	Fennell et al., 2022[1] BNF NHS Reference Costs[15] PSSRU[16]

Abbreviations: ASC, active symptom control; PFS. Progression free survival; OS, overall survival; SOC, standard of care.

The estimated initial utility was 0.62, with a utility of 0.506 upon progression, and 0 utility at death. PFS gain was estimated to be 1.4 months (0.1167 years), the difference between vinorelbine and ASC median PFS from VIM. Adjusting for quality of life (using the utility difference of 0.114) generated a quality adjusted life year gain from PFS of 0.0133. Overall survival gain was

estimated to be 0.2 months (0.01667 years), the difference between vinorelbine and SOC median overall survival from VIM. Adjusting for quality of life (using a utility value of 0.506) generated a QALY gain from overall survival of 0.00843.

This generated a total QALY gain of 0.022 (derived from considering the extension to median PFS and overall survival for vinorelbine compared to SOC). The estimated ICER was £197,669 (BNF medicine list prices, £4,296/0.022).

Scenario analyses considered adjustment to the limited number of parameters considered in the simple analysis (Table 4). The utility values for subsequent progression created variation in the estimated ICER. The closer the subsequent progression utility value was to 0, the lower the estimated ICER, as the PFS improvement became a greater contributor to the QALY gain.

Table 4 | Summary of base case and scenario analysis results (BNF medicine list prices)

	Base case	Scenario	Inc. cost	Inc. QALYs	ICER
Base case	-	-	£4,296	0.0217	£197,669
1a	Patients enter with utility 0.62 with progressed utility 0.506	Progressed utility set to 0.465	£4,296	0.0258	£166,297
1b		Progressed utility set to 0.31	£4,296	0.0413	£103,935
1c		Progressed utility set to 0 (QALY gain is all from PFS)	£4,296	0.0723	£59,392
2a	Vinorelbine 4.2 months PFS. SOC 2.8 months PFS.	PFS upper bound SOC and vinorelbine	£8,962*	0.0455	£197, 039
2b		PFS lower bound SOC and vinorelbine	£1,955*	0.016	£121,933

Abbreviations: Inc, incremental; PFS, Progression free survival; OS, overall survival; SOC, standard of care. *In these scenarios the treatment costs are scaled in relation to the progression free survival.

From these results, it is unlikely this intervention will be cost-effective at accepted thresholds, with an estimated ICER of approximately £198k. The lowest ICER estimate of £59k assumes a large quality of life advantage for PFS, with later progression equivalent to death.

The significant limitation of these estimates is that they are derived from a simple model using a limited set of summary inputs. There are also limitations of the VIM outcome data, such as ASC arm crossover to vinorelbine, and patients from both arms receiving subsequent immunotherapies (including through enrolment in CONFIRM). Given this simple analysis these confounding factors cannot be addressed, increasing uncertainty in the generalisability of results in NHS Scotland.

These ICERs are exploratory in nature, are subject to limitations, and should be seen as a guiding estimate. However, they do illustrate the range where the ICER could potentially be, with estimates providing indicative support that the intervention is not cost effective.

Summary

The cost-comparison highlights that vinorelbine is a cost increasing intervention. There were no published ICERs available. However, an exploratory cost-utility analysis estimated ICERs that were significantly higher than accepted thresholds.

If vinorelbine is not cost-effective, then less total population health gain is achievable, as the resources could have been used to acquire an intervention to deliver greater health benefit.

8. Council review | Cost-effectiveness evaluation

As the clinical benefit-risk balance was insufficient to support the use in the full proposed patient population, the council could not support the cost-effectiveness evaluation.

9. Service Impact

Up to 10 patients per year are expected to be eligible for oral vinorelbine in Scotland. These patients may represent an additional patient population depending on current treatment practices for second-line and beyond MPM. Prior to administration, patients are required to have weekly blood tests.

10. Budget Impact

NCMAG is unable to publish the budget impact due to commercial in confidence issues.

11. Acknowledgements

NCMAG would like to acknowledge the patient group partners, Mesothelioma UK and Action on Asbestos, for their invaluable input.

We would also like to acknowledge the data provided by the Cancer Medicines Outcomes Programme, which provided very helpful context for this proposal, and the VIM study team for providing supporting study data.

This advice represents the view of the NCMAG Council 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.

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Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by