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|  | ***The VINO ectopic trial*** |

**Study Protocol:**

Clinical trial of oral vinorelbine to treat women with ectopic pregnancy

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| Sponsor | The University of Melbourne – Department of Obstetrics and Gynaecology |
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# PROTOCOL APPROVAL

**The VINO ectopic Trial:**

*Clinical trial of oral vinorelbine to treat women with ectopic pregnancy*

Health and Disability Ethics Committee project number – 17/CEN/155

Australianand New Zealand Clinical Trials Registry (ANZCTR) number - ACTRN-1261-7001-1183-92p

# PROTOCOL APPROVAL (Cont.)

**The VINO ectopic Trial:**

*Clinical trial of oral vinorelbine to treat women with ectopic pregnancy*

Health and Disability Ethics Committee project number –17/CEN/155

Australianand New Zealand Clinical Trials Registry (ANZCTR) number - ACTRN-1261-7001-1183-92p

# LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ANZCTR | Australian and New Zealand Clinical Trials Registry |
| CARM | Centre for Adverse Reactions Monitoring |
| CRF | Case Report Form |
| EPC | Early Pregnancy Clinic |
| FBE | Full Blood Examination |
| GCP | Good Clinical Practice |
| hCG | Human Chorionic Gonadotrophin |
| HDEC | Health and Disability Ethics Committees |
| IB | Investigator’s Brochure |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product |
| ISF | Investigator Site File |
| IVF | In vitro fertilisation |
| LFT/LFTs | Liver Function Tests |
| NSH | North Shore Hospital |
| NZNPC | New Zealand National Poisons Centre |
| O&G | Obstetrics and Gynaecology |
| PI | Principal Investigator |
| PICF | Patient Information and Consent Form |
| PID | Pelvic Inflammatory Disease |
| SAE | Serious Adverse Event |
| SADR | Serious Adverse Drug Reaction |
| SCOTT | Standing Committee on Therapeutic Trials |
| SOP | Standard Operating Procedure |
| STI/STIs | Sexually Transmitted Infection(s) |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| TSC | Trial Steering Committee |
| UADR | Unexpected Adverse Drug Reaction |
| U&E/U&Es | Urea and Electrolytes |

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# TRIAL SUMMARY

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| DESIGN: | An early (phase II), investigator-led, unblinded, single-arm, proof-of-concept clinical trial to assess the safety, toxicity and tolerability profiles of oral vinorelbine as a treatment for women with stable ectopic pregnancies |
| SETTING: | A single, public hospital offering emergency on-call Obstetrics and Gynaecology (O&G) services (North Shore Hospital (NSH) - Auckland, New Zealand). |
| TARGET POPULATION: | 20 women who present to NSH’s Early Pregnancy Clinic (EPC) and are diagnosed with stable ectopic pregnancies. Each recruited participant will receive two doses of 60mg/m² of oral vinorelbine, one week apart.  **INCLUSION CRITERIA FOR THE STUDY:**  Women who have/who are:   * Aged 18-50 years old * English speaking * Able to provide informed consent to participate * A diagnosis of a tubal ectopic pregnancy on transvaginal ultrasound * A clinically stable ectopic pregnancy (no evidence of bleeding or rupture) * A pre-treatment serum Human Chorionic Gonadotrophin (hCG) level of 300 – 3,000 IU/L * Adnexal mass ≤3.5 cm * No fetal cardiac activity detected on ultrasound   **EXCLUSION CRITERIA FOR THE STUDY:**  Women who have/who are:   * Unable to provide informed consent to participate * Women with a pregnancy of unknown location (PUL) or heterotopic pregnancy * Evidence of significant intra-abdominal bleed on ultrasound, defined by echogenic free fluid above the uterine fundus or surrounding ovary. * Contraindication(s) to vinorelbine or to medical management of ectopic pregnancy * Immunodeficiency disorder(s) * A current malignancy * Received chemotherapy or radiation therapy in the previous five years * Concomitant disease which could significantly impair gastric absorption (Inflammatory bowel disease, coeliac, etc.) * History of surgical resection of the stomach/small bowel * Breastfeeding * Hepatic impairment, renal impairment, or haematological toxicity |
| HEALTH TECHNOLOGIES ASSESSED: | All recruited participants will receive 2 doses of 60mg/m² of oral vinorelbine (traded as Navelbine®, spaced one week apart (see *Appendix 1*: *Medsafe Information for Healthcare Professionals - Navelbine® oral*) |
| OUTCOME MEASURES: | **PRIMARY OUTCOMES:**  To establish the safety, toxicity and tolerability profiles of oral vinorelbine therapy in patients presenting with stable ectopic pregnancies.  **SECONDARY OUTCOMES:**  To determine the efficacy of oral vinorelbine therapy as a treatment to resolve ectopic pregnancies (defined as the percentage of successfully treated participants who do not go on to require salvage surgery); to assess the return to normal menses following vinorelbine administration; and to assess subsequent fertility, pregnancy and birth outcomes for women receiving oral vinorelbine as a treatment for ectopic pregnancy |
| ANALYSIS: | 1. As there is no comparison arm, clinical variables and the clinical course will be presented as descriptive statistics 2. There is no power calculation to perform 3. Clinical outcomes of participants will be compared with a contemporaneous cohort 4. Continuous variables will be statistically analysed using t-tests (parametric) or Mann-Whitney U tests (non-parametric), as appropriate 5. Categorical variables will be statistically analysed using chi-squared or Fisher’s exact tests, as appropriate 6. Statistical analysis will be performed using *GraphPad Prism 6* (GraphPad Software, La Jolla, CA) 7. A p value of <0.05 will be considered statistically significant. |
| SAMPLE SIZE: | The researchers plan to recruit 20 women with stable ectopic pregnancies over an 18-month period, or until recruitment has been exhausted. |

# 

# LAY SUMMARY

Ectopic pregnancies are pregnancies that occur outside of the womb, with the vast majority located in the Fallopian tube (the tube which carries a fertilised egg to the womb). They are potentially life threatening as they can erode maternal blood vessels and cause fatal internal bleeding. They are relatively common, representing around 2% of pregnancies.

If an ectopic pregnancy is identified early and is small in size, a drug called methotrexate can be administered via injection. However, only a small number of ectopic pregnancies (~25%) are identified early enough to be suitable for this medication. Additionally, methotrexate is unsuccessful in treating ectopic pregnancies in up to 30% of cases. This means that the majority of ectopic pregnancies are ultimately removed surgically. This exposes many affected women to both surgical and anaesthetic risks; is complex (requiring doctors with specialist surgical skills); and can involve the removal of the woman’s Fallopian tube. As fertility preservation is an important concern in this area of medicine, the development of a new medical therapy with a higher success rate than methotrexate would be a major advance in the clinical care of women who have ectopic pregnancies.

Excitingly, we have discovered in pre-clinical laboratory studies that vinorelbine, an orally available chemotherapeutic medication, may be appropriate for use as an alternative to methotrexate in the medical treatment of ectopic pregnancies. Specifically, we have found in our laboratory studies that vinorelbine is 1,000 to 10,000 times more effective than methotrexate at killing placental cells, is more effective than methotrexate in an animal model ectopic pregnancy, does not cause cell death of donated human Fallopian tubes and does not impact upon subsequent breeding in mice (after a four week washout period). Together, these findings indicate that vinorelbine may not impede future fertility, and that may be an efficacious treatment for ectopic pregnancy.

Given these promising pre-clinical results, we hope to progress this concept and eventually translate these laboratory findings into clinical care. We propose to begin this process with a *proof-of-concept,* early phase clinical trial. We will recruit 20 women with stable ectopic pregnancies and treat the participants with two doses of 60mg/m² of oral vinorelbine, spaced one week apart. We will assess the safety, toxicity and tolerability of vinorelbine therapy in these women, as well as monitoring the effectiveness of vinorelbine in killing placental cells and resolving ectopic pregnancies. If successful, we will gain sufficient evidence to progress our investigations of vinorelbine as a treatment for ectopic pregnancies to a large-scale, randomized clinical trial. We hope that it may form the basis for an efficient and safe future medical treatment option for this group of women who do not wish to undergo surgery or have their tube removed. This could lead to improvements in the health and future fertility outcomes of women who experience this common, potentially life-threatening pregnancy complication.

1. **INTRODUCTION**
   1. **BACKGROUND**
      1. **Ectopic pregnancy**

Ectopic pregnancies represent 1-2% of all human pregnancies and are a leading cause of maternal death in the first trimester of pregnancy [1, 2]. They are characterized by the extra-uterine implantation of a pregnancy, with the vast majority (95-98%) occurring in the Fallopian tube [1, 3]. Risk factors for developing an ectopic pregnancy include Pelvic Inflammatory Disease (PID); presence of chlamydia or other sexually transmitted infection (STI); a previous ectopic pregnancy; in vitro fertilisation (IVF); history of tubal surgery; and cigarette smoking [1-5]. If an ectopic pregnancy grows beyond a certain size, it can erode the surrounding maternal tissues and vasculature, which can lead to a rupture through the wall of the affected tube. This can cause significant and life-threatening maternal blood loss. Tubular ectopic pregnancies constitute a major obstetric and gynaecological complication given that they occur relatively frequently, combined with the significant risk that they pose to the health and future fertility of affected women. It is important to note that ectopic pregnancies are non-viable and that the sole consideration in this treatment scenario is the health and wellbeing of the mother.

* + 1. **Current management**

There are two current treatment options for the active management of an ectopic pregnancy – surgical excision consisting of either a salpingectomy (removal of the entire Fallopian tube) or a salpingostomy (partial removal of the affected tube); or medical management using methotrexate to resolve the ectopic pregnancy [1, 5-7]. Surgical management of an ectopic pregnancy remains the standard of treatment and is the only appropriate option where there is any evidence of tubular rupture, haemodynamic instability, active bleeding, where medical management is contraindicated or has previously been unsuccessful [1]. Around 18% of women with ectopic pregnancies require urgent surgical intervention for a tubular rupture [8].

The remainder of stable ectopic pregnancies could be appropriate for consideration of a more conservative treatment option than surgery (either medical or expectant management). Medical management of a stable ectopic pregnancy may be the preferred option for women who do not wish to undergo surgery, those with various anaesthetic risk factors or for whom preservation of their Fallopian tube and future fertility is of great importance.

Methotrexate is the only drug that is currently approved to treat ectopic pregnancy. It is a folic acid antagonist, interfering with DNA synthesis and cell proliferation [1, 5]. Ideally, this drug halts the growth and begins the destruction of the embryonic and placental cells, effectively dissolving the ectopic pregnancy. However, methotrexate therapy can take several weeks to resolve an ectopic pregnancy and failure rates have been reported in up to 29% of single-dose recipients [5, 9]. Many of these women for whom methotrexate treatment has been unsuccessful then go on to require salvage surgery in order to remove the ectopic pregnancy (and with it, the Fallopian tube) [1]. This group of women are therefore exposed to two sets of iatrogenic risk – firstly, to the risks of taking methotrexate, compounded by the risks of having a subsequent surgery.

* + 1. **Developing a better medical treatment for ectopic pregnancy**

Ectopic pregnancies are a leading cause of global maternal death and illness in the first trimester. These negative health impacts are disproportionately experienced by women in remote communities, developing countries and other resource-poor settings, where access to emergency surgical treatment and safe medical care can be manifestly inadequate (if it is available at all) [1, 4]. Despite the significant and inequitably shared impacts of ectopic pregnancy on population health outcomes, there appears to be a distinct shortage of medical alternative therapies currently being investigated at both the pre-clinical laboratory and human clinical trial levels. Given the limitations and relatively high failure rate of intramuscular methotrexate therapy, and the enormity of the impacts of ectopic pregnancies on maternal health, it is imperative that new potential medical therapies for this common obstetric complication are rigorously investigated.

* 1. **RATIONALE FOR THE STUDY**
     1. **Potential new medical therapeutic option for ectopic pregnancy – vinorelbine**

Vinorelbine is a chemotherapeutic medication that is currently indicated for use in the treatment non-small cell lung cancer, late stage breast and ovarian cancer and Hodgkin’s lymphoma (see *Appendix 1*). Vinorelbine is considered to be a safe and well tolerated chemotherapeutic. Vinorelbine was first manufactured in 1979 [10], meaning that there is several decades’ of data relating to its use in human cancer patients, including extensive information about contraindications, known potential adverse reactions and other safety considerations. Vinorelbine induces cytotoxicity by binding to tubulin, which disrupts mitotic spindle formation and results in the arrest of the cell cycle, ultimately leading to apoptosis of mitotic cells, thus targeting dividing and highly proliferative cells [10]. Given the placenta is highly proliferative during the first trimester of pregnancy but the Fallopian tube is not, it is plausible that vinorelbine could be efficacious in resolving an ectopic pregnancy whilst minimally affecting the surrounding tube.

Interestingly, there are a number of relative similarities between cancer cells and placental cells [11]. Both undergo a process of rapid proliferation and self-replication leading to growth – in cancer patients, this is demonstrated by an increase in the physical size of an untreated cancer. Similarly, in the first weeks of a pregnancy, the initial placental cells split and copy themselves, quickly developing into a growing embryo. Given these parallels in the nature of the cycles of cancer and placental cells, we examined whether vinorelbine could also potentially be effective in killing placental cells in the laboratory, interrupting some key features of the ectopic pregnancy disease process.

* + 1. **Pre-clinical laboratory observations**

Our pre-clinical investigations delivered some promising findings. Firstly, we found that vinorelbine was 1,000-10,000 times more effective than methotrexate alone, and still significantly more potent than methotrexate combined with gefitinb, at killing placental cells *in vitro* (combination methotrexate and gefitinib is another proposed medical treatment for ectopic pregnancies, currently being evaluated in a phase III clinical trial in the UK). Secondly, our *in vitro* studiesshowed that donated human Fallopian tube samples treated with vinorelbine did not display up-regulation of apoptosis molecules (i.e. no evidence of Fallopian tube cell death). This means that although vinorelbine was observed to efficaciously kill placental cells, vinorelbine did not appear to induce cell death in human Fallopian tubes *ex-vivo*. Importantly, this finding indicates that placental cells may be exquisitely sensitive to vinorelbine.

In our *in vivo* mouse studies, vinorelbine was again more efficacious than methotrexate and combination methotrexate and gefitinib at reducing placental xenografts in mice. Additionally, four weeks after exposure to vinorelbine, mice in our *in vivo* studies were allowed to breed. These mice displayed normal fertility, with no difference in serum markers of ovarian reserve, litter size, pup birth weight and placental weight between control and vinorelbine-treated mice. Together, our pre-clinical studies show strong preliminary evidence that the use of vinorelbine may be significantly more efficacious than methotrexate at resolving ectopic pregnancy *without affecting future fertility*.

* + 1. **Progressing the concept of vinorelbine as a potential treatment**

Given the promising *in vitro* and *in vivo* data, coupled with vinorelbine’s established safety and tolerability profiles in the treatment of human oncology patients, we now wish to progress this concept to the clinic. We hope to recruit 20 participants with stable ectopic pregnancies and treat them each with 2 doses of 60mg/m² of oral vinoralbine, spaced one week apart, instead of methotrexate. The primary aims of this study are to assess the safety, toxicity and tolerability profiles of vinorelbine when administered exclusively to a cohort of women with stable ectopic pregnancies.

Secondly, we will assess key clinical and biochemical features of the resolution of an ectopic pregnancy in women receiving vinorelbine therapy. If effective, this will provide the first evidence that vinorelbine may be a safe and efficacious tablet-only treatment for stable ectopic pregnancies in humans. If the data from this study is promising, it will form the basis for a large, randomized controlled trial aiming to establish oral vinorelbine as a standard medical treatment option for stable ectopic pregnancies.

* 1. **POTENTIAL RISKS TO PARTICIPANTS** 
     1. **Possible maternal risks**

Patients with ectopic pregnancies may experience discomforts or inconveniences relating to their admission to hospital, clinical examinations and blood tests, regardless of whether or not they decide to participate in the study. However, patients recruited to the study would undergo additional examinations and pathology tests that are supplementary to their routine clinical care, and as such, may experience an increase in these discomforts and inconveniences. These additional study requirements will be outlined in detail to all potential participants during the informed consent process.

We expect the proposed treatment will be safe and generally well tolerated in this cohort of otherwise-well women. Vinorelbine is a chemotherapeutic drug which is currently taken on a long-term basis by many people with particular cancers, while we propose to administer two doses per participant in totality. However as with any medication, participants may experience allergic reactions or other side effects from taking vinorelbine. Given that the cohort of women who we propose to enrol in this study will not have concomitant cancer diagnoses, are not immunocompromised, and will not be taking the drug on a long term basis, the risk of developing these side effects may be somewhat mitigated. Participants in this study will still be closely monitored to ensure their ongoing safety.

Known potential side effects of vinorelbine therapy in oncology patients include gastrointestinal symptoms, respiratory distress, agranulocytosis and neutropaenia. The long-term carcinogenic potential in humans of vinorelbine has not been established (nor has it been for the current standard treatment, methotrexate). There is no data about the excretion of vinorelbine into human breast milk, so its use should be avoided in women who are breastfeeding (see *Appendix 1*).

* + 1. **Possible fetal risks (subsequent pregnancies)**

Vinorelbine is a ‘Category D’ drug, which has been shown to cause damage to the developing fetus in animal studies. There are no studies into its effects on human pregnancies, although it is reasonable to infer that vinorelbine carries a significant potential risk of harm to the human fetus (see *Appendix 1*). Participants who receive any amount of vinorelbine for this study will be counselled about these risks, with the conservative advice that they should avoid a subsequent pregnancy for at least 3 months following their most recent vinorelbine dose.

*\*\*Note - There is no defined, recommended timeframe between ceasing vinorelbine therapy and the safe conception of a subsequent pregnancy (see Appendix 1). However, advising a 3 month wait is consistent with the advice currently given to women following methotrexate therapy (a ‘Category X’ chemotherapeutic agent) for the treatment of an ectopic pregnancy.*

* 1. **POTENTIAL BENEFITS**
     1. **Safe, effective treatment; better health outcomes for women**

There are some potential benefits for participants related to their participation in the study. We hope to completely resolve ectopic pregnancy using a well-tolerated, orally-available medication with an established low-risk harm profile in humans. Potential maternal benefits include disease stabilisation, as well as reductions in both medical management failure and the number of cases that progress to haemodynamic instability, internal bleeding and tubular rupture. This would ultimately reduce the number of women having operative treatment for their ectopic pregnancies, lowering community exposure to the potential inherent risks associated with anaesthesia and surgery. Additionally, reductions in the number of salpingectomy/salpingostomy procedures being performed may have a positive influence on future fertility preservation for women with ectopic pregnancies.

If we are successful at gaining preliminary evidence that vinorelbine is a safe, efficacious, non-surgical option for the treatment of women with ectopic pregnancies, the impact on reducing the numbers of surgical interventions could be two-fold. Firstly, we anticipate that we may see a major decrease in the incidence of failed medical management of ectopic pregnancies, reducing the number of women who will then require a subsequent salvage surgery. Additionally, if we can show that vinorelbine has a higher success rate than methotrexate, there may be a greater uptake of women electing to have their ectopic pregnancies medically managed in the first place. Given the relative frequency of ectopic pregnancies, even a slight reduction in the proportion of cases requiring surgical intervention could carry significant latent benefits. Broadly, vinorelbine treatment has the potential to reduce the surgical and anaesthetic risk profiles in the population of women who experience ectopic pregnancies; may preserve their future fertility in relation to Fallopian tube conservation; and have significant impacts on reducing surgery and inpatient-related costs incurred by individuals, families, health services and health systems.

* + 1. **Cost benefits**

The surgical management of an ectopic pregnancy incurs a range of direct and indirect costs, making them an expensive use of health care resources [1]. These expenses are substantial regardless of the surgical technique, with the costs of the specialised instruments used for a laparoscopic procedure rivalling the costs associated with multi-day patient admissions following an open laparotomy procedure.

A specific economic modelling or cost-benefit analysis of offering methotrexate as a medical treatment for ectopic pregnancies has not been performed for the Oceania region in recent years. This type of assessment would be useful to better inform health services of resource allocation and budgetary considerations when offering methotrexate therapy to this cohort of women. When successful, the medical management of an ectopic pregnancy has been shown to be a cost-effective alternative when compared directly to surgery [1]. However, given the relatively high number of methotrexate recipients who then go on to require subsequent surgical intervention after an intensive period of specialist outpatient follow-up, this comparison is perhaps not quite so clear. The total cost of inevitably treating a certain number of women every year with both failed methotrexate and a salvage surgery significantly reduces any economic benefits gained in the first place.

A medical therapy that has a higher success rate than methotrexate at resolving ectopic pregnancies therefore has the potential to save significant costs, reducing the economic impact and pressure on finite resources within individual health services and national health systems from treating this cohort of women.

* + 1. **Reduction of maternal mortality in developing countries**

Continued global efforts to promote women’s agency and ongoing increases in women’s and girls’ access to healthcare, education, contraception, and legal and governmental representation remain the most effective way to improve global maternal morbidity and mortality outcomes. However, research into new treatments for ectopic pregnancies could also make a significant contribution, especially if these treatments could be translated into a variety of different economic settings. There is a distinct shortage of available epidemiological data examining the global burden of disease of ectopic pregnancies, and information that is available is often presented inconsistently, making the drawing of comparisons and accurate conclusions about the effects of the disease on population health somewhat difficult [1, 4]. Published data and statistics that attempt to capture epidemiological information about ectopic pregnancies may be interchangeably presented as a yearly incidence rate; as a proportion of all live births; as a proportion of all stillbirths, miscarriages and live births combined; or simply commented on as a potential outcome of STIs and PID [4]. Despite these ambiguities, it has been established that:

* Each day, there are approximately 830 maternal deaths globally attributed to preventable causes in pregnancy and childbirth [12]
* Approximately 99% of maternal deaths occur in developing countries [12]
* Ectopic pregnancy is a leading cause of maternal death and illness in the first trimester [1]
* Women who do not have ready access to specialist medical and surgical health care to treat ectopic pregnancies are more at risk of becoming ill or dying than women with better access to specialist health resources [4, 12]
* Women in remote communities or developing countries who have difficulty accessing medical assessment, diagnosis and treatment for sexually transmitted diseases (such as gonorrhoea, chlamydia and syphilis) are more at risk of developing pelvic inflammatory disease, and subsequently experience a higher burden of ectopic pregnancy [4]

It is an important aspect of publically-funded research for the investigators to consider how any positive findings might be equitably translated for use into different populations and across various health care contexts, such as in rural and remote communities, developing countries and other resource-poor settings. Vinorelbine is a medication already known to have a low-risk harm profile; is generally well-tolerated; and is readily available. Vitally, for resource-poor or remote settings, vinorelbine is also produced generically in an intravenously injectable form, which does not require refrigeration to maintain its molecular stability. If vinorelbine can be established as a safe and effective treatment for stable ectopic pregnancies, it could be realistically translated into use in isolated communities within the Oceania region, as well as being potentially appropriate for use in developing countries. However, more standardised epidemiological research into the impacts of ectopic pregnancies is needed to truly capture the magnitude of any health improvements achieved through the introduction of new medical therapies.

1. **STUDY OBJECTIVES**

Currently, there are both a medical and a surgical treatment option available to women to resolve a stable ectopic pregnancy. The surgical option involves the removal of all or a part of the affected Fallopian tube (salpingectomy and salpingostomy, respectively); is a costly treatment; and exposes women to the inherent risks involved with having an anaesthetic and a surgery. The current medical treatment option has a reasonably high failure rate of around 30% [9]. An early (phase II) clinical trial assessing the safety, toxicity and tolerability profiles of vinorelbine in patients with ectopic pregnancies is required to assess the potential suitability of vinorelbine as a new, safe, efficacious and cost-effective therapeutic treatment option for women with stable ectopic pregnancies.

* 1. **OBJECTIVES**
     1. **Primary objectives**

The primary objectives of this study are to establish the safety, toxicity and tolerability profiles of vinorelbine, specifically in patients with stable ectopic pregnancies. In particular, we will be examining:

* Any adverse effects in the treated participants (safety data)
* Participants’ serial blood tests, including Full Blood Examinations (FBE); Urea and Electrolytes (U&Es); and Liver Function Tests (LFTs) (safety and toxicity data)
* Participants’ evaluations on the acceptability of vinorelbine treatment, including its administration, side effects and follow up requirements (tolerability data)
  + 1. **Secondary objectives**

To determine the effects of vinorelbine therapy on the clinical outcomes, biochemical markers and subsequent fertility of participants by assessing for:

* Length of time from treatment initiation to resolution of ectopic pregnancy (defined as hCG <5IU/L or requiring surgical removal of fallopian tube).
* Occurrence of clinical symptoms of medical management failure; i.e. evolving tubular rupture (haemodynamic instability; abdominal pain; or a persistently raised hCG after Day 7).
* Length of time from vinorelbine treatment to participants’ return to normal menses
* Subsequent fertility, pregnancy and birth outcomes for participants (limited to a two year follow-up period from recruitment of the first participant)
  1. **ENDPOINTS**
     1. **Primary endpoint**

The end (resolution) of the ectopic pregnancy – either when serum hCG levels return to <5 IU/L or when the pregnancy is surgically excised.

* + 1. **Secondary endpoints**

Laboratory endpoints/measures of interest:

* Serum biomarkers of ectopic pregnancy during disease progression (serial hCG measurements)
* Biochemical indices of liver and renal function (Urea and Electrolytes (U&Es) and Liver Function Tests (LFTs))
* Measures of haematological toxicity (e.g. neutropaenia) on FBE

Clinical endpoints/measures of interest:

* Adverse Events (AEs) in the participants
* Time (days/weeks) to resolution of ectopic pregnancy following administration of vinorelbine
* Incidence of failed medical management reverting to surgical management
* Emergence of or change in clinical symptoms of ectopic pregnancy (increased pain, hypotension, etc.)
* Acceptability of treatment and side effects to participants
* Time (weeks/months) for participants to return to normal menses
* Subsequent fertility, pregnancy and birth outcomes for participants

1. **STUDY DESIGN**

This study is an early (phase II), unblinded, single-arm, proof-of-concept clinical intervention trial aiming to assess the safety, toxicity and tolerability profiles of vinorelbine as a medical treatment option for women with stable ectopic pregnancies.

20 participants with singleton, tubular ectopic pregnancies will be recruited over an estimated 12-18 month period from the EPC at North Shore Hospital in Auckland.

All recruited participants will receive an initial dose of 60mg/m² of oral vinorelbine. Participants will receive a second, identical dose one week later. The dose will be rounded to the nearest whole number. The tablets are available in 20 mg and 30 mg preparations in New Zealand (see *Appendix 1*).

The following treatment and pathology collection schedule will be followed during the course of participants’ treatment of their ectopic pregnancies:

|  |  |
| --- | --- |
|  |  |
|  |
| *\*Note: the treatment schedule above mirrors normal clinical management of women undergoing medical management of an ectopic pregnancy, with the exception of some protocol-specific blood tests (FBE, U&Es and LFTs collected on Day 4 and the potential additional serum hCG level on Day 11). These additional tests have been added to the treatment protocol as an extra safeguard for women participating in this study, given that this treatment is still under investigation.* |

The decision to admit a participant to hospital for inpatient observation, to withdraw a participant from the trial and revert to surgical management, or to continue with medical management will be assessed at every point of contact that the participants have with North Shore Hospital. These decisions will be made by the treating physician in charge of the EPC (Dr Prathima Chowdary or Dr Ngaire Anderson), in consultation with their EPC clinical colleagues (as indicated), and following discussion with the participant.

The NSH’s guidelines, protocols and local Standard Operating Procedures (SOP) of the medical management of women with stable ectopic pregnancies (including serial blood tests and transvaginal ultrasounds) - or management as otherwise ordered by the treating clinicians – will be followed.

Participants will be actively monitored by members of the research and EPC teams for signs and symptoms of clinical deterioration, adverse outcomes or possible side-effects of vinorelbine during their time spent in the EPC. The participants’ ongoing willingness to continue with the study will be verbally confirmed at each point of contact with the research team.

A member of the research team will be on call to attend or for advice relating to concerns raised by the participants or the clinicians providing their direct care. Additionally, participants will be given a 24 hour contact number of the on-call EPC doctor in case of a clinical deterioration outside of hospital, which is a standard safety measure for all women while they are receiving medical or expectant treatment for an ectopic pregnancy.

Blood tests and other pathology results will be monitored by clinicians as a part of routine care. The researchers will also have access to and review these routine pathology results – this data forms some of the secondary outcomes of the study.

Any deviations from routine clinical care will be determined by the treating clinician or unit. In the case where a member of the research team is also acting as the treating clinician, these decisions will be made in consultation with other members of the clinical care team, with the best interests of participant as the paramount consideration.

Researchers will contact participants by phone at 3, 6, 12, 18 and 24 months following the completion of their course of vinorelbine to assess for their return to normal menses, to collect subsequent fertility, pregnancy and birth data, and to assess the long-term acceptability of vinorelbine therapy as a medical treatment option for stable ectopic pregnancies.

1. **STUDY POPULATION**
   1. **NUMBER OF PARTICIPANTS**

The researchers plan to recruit 20 women with stable ectopic pregnancies over a period of 12-18 months. The researchers believe that this sample size is justified, as outlined in *Section 9.1* of this document.

* 1. **INCLUSION CRITERIA**

**INCLUSION CRITERIA FOR THE STUDY:**

Women who have/who are:

* Aged 18-50 years old
* English speaking
* Able to provide informed consent to participate
* A diagnosis of a tubal ectopic pregnancy on transvaginal ultrasound
* A clinically stable ectopic pregnancy (no evidence of bleeding or rupture)
* A pre-treatment serum Human Chorionic Gonadotrophin (hCG) level of 300 – 3,000 IU/L
* Adnexal mass ≤3.5 cm
* No fetal cardiac activity detected on ultrasound
  1. **EXCLUSION CRITERIA**

**EXCLUSION CRITERIA FOR THE STUDY:**

Women who have/who are:

* Unable to provide informed consent to participate
* Women with a pregnancy of unknown location (PUL) or heterotopic pregnancy
* Evidence of significant intra-abdominal bleed on ultrasound, defined by echogenic free fluid above the uterine fundus or surrounding ovary.
* Contraindication(s) to vinorelbine or to medical management of ectopic pregnancy
* Immunodeficiency disorder(s)
* A current malignancy
* Received chemotherapy or radiation therapy in the previous five years
* Concomitant disease which could significantly impair gastric absorption (Inflammatory bowel disease, coeliac, etc.)
* History of surgical resection of the stomach/small bowel
* Breastfeeding
* Hepatic impairment, renal impairment, haematological toxicity, or other clinically significant abnormality detected in pre-treatment blood tests
  1. **CO-ENROLMENT**

Participants will not be eligible to take part in any other intervention trials from the time of giving their informed consent until their ectopic pregnancy has resolved. Participants may elect to take part in other observational research (e.g. tissue bank donations, questionnaire studies, etc.) any time, as they wish.

1. **PARTICIPANT SELECTION AND ENROLMENT** 
   1. **IDENTIFYING PARTICIPANTS**

Women who are diagnosed with a clinically stable, singleton ectopic pregnancy who present to North Shore Hospital for treatment will be identified by the research team from hospital admission data sources or referred by clinical staff in the EPC to the research team.

* 1. **CONSENTING PARTICIPANTS**

Eligible participants will be identified by their clinical care team and referred to the research team or identified by the researchers from hospital admission data. A member of the research team will approach potential participants and provide them with a verbal explanation of the study, as well as a written or electronic copy of the *Patient Information and Consent Form* (PICF).

Prior to consenting, all eligible women will have the opportunity to discuss and ask questions about the study with a member of the research team who is also a gynaecology/endosurgery doctor. Informed, written consent will only be collected once the patient has had adequate time to read and reflect upon the study information, had all questions answered to her satisfaction, and had the opportunity to discuss participation with chosen friends or family members. Women from Maori and Pasifika communities who are considering participation will additionally have the opportunity to discuss the study details with a Maori Health Liaison worker prior to being asked to provide consent.

Recruited participants will retain their copy of the PICF and be given a copy of their signed consent form for their personal records. Participants will be assigned a unique study code following their recruitment so that documents and results can be de-identified of their personal information to protect their privacy.

* 1. **SCREENING FOR ELIGIBILITY**

To be eligible for the study, a woman must have a singleton tubular ectopic pregnancy, diagnosed by transvaginal ultrasound. Additionally, the woman must meet strict inclusion and exclusion criteria, as outlined in *Sections 4.2* and *4.3*. These parameters will be applied to determine eligibility for the study for all women referred to or identified by the research team as being potentially appropriate for this study. Eligibility (or non-eligibility) should be documented by a member of the research team in the medical history of all patients screened for inclusion in the study.

* 1. **INELIGIBLE AND NON-RECRUITED PARTICIPANTS**

No further information will be collected on women once they are deemed to be ineligible to participate in the study, or once they decline or withdraw consent for their inclusion. Anonymised information will be collected on a password protected, online screening log (using REDCap software via the University of Melbourne online portal) to capture all patients assessed for their eligibility, whether or not they are recruited. Those women who are not recruited into the study or who withdraw their consent to participate will continue with standard clinical care for the treatment of their stable ectopic pregnancy, as per NSH guidelines and the treating medical unit’s instructions.

* 1. **RANDOMISATION**

Not applicable – this is a single arm, unblinded study.

* + 1. **Treatment Allocation**

Not applicable.

* + 1. **Emergency Unblinding Procedures**

Not applicable.

* 1. **WITHDRAWAL OF STUDY PARTICIPANTS**

Participation in the study is completely voluntary. Participants will be made aware of their ongoing right to discontinue taking vinorelbine or to withdraw entirely from the study at any time, and for any reason. The research team also retains the right to discontinue a participant from receiving vinorelbine and initiating their withdrawal from the study at any time, if it is deemed by the PI or lead clinician to be in the participant’s best interest(s).

If a participant is withdrawn from the study by a researcher due to a *Serious Adverse Event* (SAE), the PI will arrange for medical follow-up visits or other contact with the treating hospital until the event has been resolved or stabilised. Any data collected from the participant up until their removal from the study will still be used in statistical analyses, unless this is specifically refused by the participant.

If a participant withdraws their consent to the study at any point, no further data will be collected about them by the research team. However, permission will be sought to continue using anonymised data and research samples collected from the participant up until the point of withdrawal. The research team will attempt to identify with the participant the reason/s for their withdrawal, in case a study protocol amendment and/or medical follow-up visits are warranted.

The research team will make reasonable attempts (i.e. attempting to make contact on ≥3 occasions, using more than one mode of communication) to locate a participant before they are deemed to be ‘lost to follow-up’. If a participant is deemed to be lost to follow-up, but has not indicated to the research team that they wish to be withdrawn from the study, their anonymised data and any collected samples will still be used in the final analysis.

1. **INVESTIGATIONAL MEDICINAL PRODUCT** 
   1. **STUDY DRUG**

Generic: Vinorelbine

Traded as: Navelbine® Oral 20 mg and Navelbine® Oral 30 mg (Pierre Fabre Ltd.)

Schedule: S4

* + 1. **Study drug identification and presentation**

Navelbine® oral (vinorelbine tartrate) – supplied in blister packs of 1 tablet.

Physical description:

20 mg tablets - Light brown, soft gelatine capsule, printed with ‘*N20’.*

30mg tablets – Pink, soft gelatine capsule, printed with *‘N30’*.

(see *Appendix 1*).

* + 1. **Study drug manufacturer**

Pierre Fabre Médicament – Plantes et Industrie

16 Rue Jean Rostand

Gaillac

FRANCE 81600

Tel: +33 5 6381 2400

Web: <https://www.pierre-fabre.com/en>

* + 1. **Medsafe (NZ) and Australian Register of Therapeutic Goods (ARTG) product detail**

|  |  |
| --- | --- |
| Medsafe file reference: TT50-5769/1  Drug sponsor:  New Zealand Medical and Scientific Ltd.  PO Box 132400  Sylvia Park  Auckland  NEW ZEALAND 1644  Tel: +64 9 259 4062  Web: <http://www.nzms.co.nz/> | ARTG ID: 99557  Drug sponsor:  Pierre Fabre Australia Pty. Ltd.  PO Box 6493  North Sydney  NSW  AUSTRALIA 2059  Tel: +61 2 9195 6200  Web: <https://www.pierre-fabre.com/en/implantations/australia> |

* + 1. **Supply**

The NSH clinical trials pharmacy will supply vinorelbine to the EPC for use during this trial with project funds. A small stock will be securely kept in the refrigerator in the EPC, so that it is quickly accessible when required for administration to a trial participant. After each administration, the researchers will send a notification to the pharmacy, requesting that the dispensed stock be replaced. It is anticipated that this system will assist with pharmacy record keeping, keep wastage of stock to a minimum, be minimally disruptive to the normal operations of the EPC and pharmacy, as well as allowing for the trial medication to be readily available if it is needed outside of the pharmacists’ normal working hours.

* + 1. **Labelling and packaging**

Vinorelbine will be supplied to the EPC in accordance with the local hospital SOP and any relevant NZ legislation for prescription study medication labelling and packaging. As this is not a blinded study, vinorelbine can still be identified by its generic name, trade name and dose on the packaging/label.

* + 1. **Storage**

Vinorelbine will be securely stored onsite at NSH as per local SOP. The NSH pharmacy may elect to keep dispensing logs. The vinorelbine will be refrigerated, as per the manufacturer’s instructions (see *Appendix 1*) between 2˚ to 8˚ C, until it is removed for administration to a participant. The EPC will keep a log of the date, time, dosage and number of tablets administered to the relevant participant’s unique study code, which can be compared with pharmacy records in case of an internal or regulatory audit. Any unused vinorelbine from the supply dispensed to the EPC will be returned to the local hospital pharmacy at the conclusion of the study, or when the medication expires.

* + 1. **Manufacturer’s Product Information/Investigators Brochure (IB)**

Madsafe’s reviewed summary of the manufacturer’s Product Information for vinorelbine (traded as Navelbine® Oral) is given in *Appendix 1*.

* 1. **DOSING REGIME**

Each trial participant is expected to receive a total of 2 doses of 60mg/m² of oral vinorelbine, to be administered one week apart. A repeat serum hCG level will be performed on Day 7 prior to the administration of the second dose of vinorelbine, in case the ectopic pregnancy has resolved and the second dose is not required.

Navelbine® Oral capsules should be swallowed whole, with a full glass of water and with food. As vinorelbine is a mucosal irritant, the capsules should not be chewed, sucked, or taken if visibly damaged.

* 1. **DOSAGE CHANGES**

A dose reduction may be appropriate in this study (i.e. the second dose will not be required if the Day 7 serum hCG level is <5 IU/L), however total dosage of vinorelbine will not exceed 2 weekly doses of 60 mg/m² per participant.

In the event that a participant withdraws from the study or is lost-to-follow up prior to taking the second dose of vinorelbine, the participant’s anonymised data and samples already collected for the study will still be included in the final analysis (unless this is specifically refused by the participant). A comment will be made on any missing data, including the reason for discontinuing with the study protocol, if it is known (e.g. participant lost to follow up; discontinued due to allergic reaction, etc.).

Any participants who experience severe side effects associated with vinorelbine therapy will be withdrawn from the study and revert to standard management of their ectopic pregnancy. See *Section 10.4.4* for definitions of event severity.

* 1. **MEDICATION PRESCRIPTION AND PARTICIPANT COMPLIANCE**

All participants in this study will be admitted as day-stay to the EPC for their serial medication administrations and check-ups. Vinorelbine will be ordered on the participants’ inpatient medication charts, as per the study protocol (60 mg/m² of oral vinorelbine, weekly, for 2 doses only). Participants will be given food and instructed to swallow the tablets whole with adequate water (as per *Appendix 1*). The timing or refusal of vinorelbine doses will be documented on the participant’s medication chart by the treating EPC nurse specialist or other clinician, as per the hospital’s local SOP for medication administration and documentation.

A member of the research team will review the patient’s medication chart to assess for compliance or deviations from the study protocol of vinorelbine administration after each relevant admission. This can be completed easily, as vinorelbine will only be administered within the hospital for this study. No take home supplies of the drug or participant medication diaries will be required.

* 1. **OVERDOSE**

There is no specific antidote for vinorelbine overdose. Overdoses of up to 10 x the recommended dose have been reported, with symptoms of toxicity consistent with known potential adverse drug reactions of vinorelbine therapy (including paralytic ileus; stomatitis; oesophagitis; bone marrow aplasia, sepsis and paresis). Fatalities following an overdose of vinorelbine have also been reported in oncology patients. Any adverse drug reactions of vinorelbine should be treated symptomatically and supportively, with appropriate treatments (blood transfusions, antibiotics, etc.) instigated at the discretion of the senior treating physician. The *New Zealand National Poisons Centre* (NZNPC) can be contacted any time by phone on 0800 764 766 for advice or information in the event of a known or suspected overdose. Additionally, information can be found on the NZNPC’s online database ([www.toxinz.com](http://www.toxinz.com)).

* 1. **OTHER MEDICATIONS**
     1. **Non-investigational medicinal products**

Analgesia and other medications will be concurrently ordered (as appropriate) for the management of this patient cohort, taking into account any medications that are contraindicated during vinorelbine therapy (see *Section 6.3.3*).

* + 1. **Permitted medications**

As outlined in Medsafe’s Information for Healthcare Professionals *-* Navelbine*®* Oral *(Appendix 1)*.

* + 1. **Other considerations and contraindicated medications**

For full information, see Medsafe’s Information for Healthcare Professionals *(Appendix 1)*. Consideration should be taken when deciding on the co-administration of vinorelbine with the following drugs:

* **Mitomycin:** Acute pulmonary reactions have been documented with the co-administration of mitomycin and vinca alkaloids (including vinorelbine).
* **Drugs with known bone marrow toxicity:** Co-administration of vinorelbine may exacerbate myelosuppressive adverse effects.
* **Warfarin:** The interaction profile of warfarin and vinorelbine are unknown. Participants who are co-administered both drugs should be monitored closely for adverse events and toxicities.
* **Cisplatin:** An increase in the incidence of granulocytopaenia has been observed with the co-administration of cisplatin and vinorelbine.
* **CYP3A4 Inducers and Inhibitors:** Vinorelbine is metabolised by cytochrome CYP3A4. The magnitude of any inducing or inhibitive effects of the co-administration of vinorelbine with CYP3A4 inducers (e.g. phenytoin) or inhibitors (e.g. ketoconazole) are unknown and should be avoided.

1. **STUDY ASSESSMENTS**

STUDY ASSESSMENTS PRIOR TO TREATMENT

As part of routine clinical care, examinations and pathology tests may have already been carried out prior to a participant’s screening for recruitment. The results of these tests and examinations may help to establish a patient’s suitability for the study and give additional details that may be pertinent to the study analysis for stratification purposes. The following test and examination results will be transcribed (as appropriate) into the *Case Report Form* (CRF), following a participant consenting for inclusion in the study:

* Gravida and parity
* Last normal menstrual period
* Height, weight and BMI
* Blood pressure readings and other observations of vital signs
* Medical progress notes tracking the history of the ectopic pregnancy and its diagnosis
* Pathology tests (including but not limited to FBE; U&Es; LFTs; hCG levels; etc.)
* Transvaginal ultrasounds – including location, size and gestational age of ectopic pregnancy

STUDY ASSESSMENTS DURING TREATMENT COURSE

A member of the research team will visit the participants at each of their day admissions to the EPC during their study to perform an assessment of the participant’s wellbeing, communicate with the EPC clinicians and review the participant’s medical history. The researcher will update the CRF detailing:

* Any AEs experienced by the participant
* Any changes in participant condition (e.g. increased abdominal pain)
* Any pathology tests undertaken since the last study visit
* Compliance with treatment regime
* Participant wellbeing
* The participant’s stated willingness to continue with the study

Other relevant information (such as earlier or subsequent blood test and ultrasound results) will be transcribed as appropriate into the CRF from patient files for the duration of the participant’s enrolment in the study.

STUDY ASSESSMENTS – DAY 0 (DAY OF FIRST TREATMENT DOSE)

* Clinical assessment – confirm the participant is not exhibiting signs or symptoms of evolving rupture, bleeding or haemodynamic instability
* Ensure standard of care pre-medication blood tests completed (FBE, U&Es, LFTs and serum hCG levels)
* Written, informed consent obtained
* Medical history review
* Discussion with participant’s treating doctors, nurses and midwives
* Eligibility confirmed by senior member of the research team
* Vinorelbine prescribed on medication chart by an O&G doctor (who is also a listed researcher)
* Vinorelbine to be administered by an appropriately qualified EPC nurse, midwife or doctor
* Assess for *Adverse Drug Reaction* (ADR) 30-180 minutes following administration of the initial dose
* Complete CRF data entry

STUDY ASSESSMENTS - DAY 4 POST-INITIAL TREATMENT DOSE

* Clinical assessment – not displaying signs or symptoms of evolving rupture, bleeding or haemodynamic instability
* Standard of care post-medical management blood test (serum hCG level)
* Additional study-specific blood tests (FBE; U&Es; LFTs) to be taken concurrently with serum hCG level
* Participant verbally expresses ongoing agreement to continue participation in the study
* Senior researcher confirms no changes to participant’s ongoing eligibility
* CRF entry completed, including assessment for ADRs/AEs

STUDY ASSESSMENTS – DAY 7 POST-INITIAL TREATMENT DOSE

* Clinical assessment – no signs or symptoms of evolving rupture, bleeding or haemodynamic instability
* Standard of care post-medical management blood tests (FBE; U&Es; LFTs and serum hCG level)
* Participant verbally expresses ongoing agreement to continue participation in the study
* Senior researcher confirms no changes to participant’s ongoing eligibility
* CRF completed, including assessment for ADRs/AEs
* Vinorelbine (2nd dose) prescribed on medication chart by an O&G doctor (who is also a listed researcher), if serum hCG level ≥5 IU/L
* Vinorelbine to be administered by an appropriately qualified EPC nurse, midwife or doctor
* Assess for *Adverse Drug Reaction* (ADR) 30-180 minutes following administration of the dose
* CRFs entry completed
* Confirm participant contact details for follow up phone calls

STUDY ASSESSMENTS - DAY 11 (IF SERUM hCG RISES BETWEEN DAYS 4-7)

* Clinical assessment – no signs or symptoms of evolving rupture, bleeding or haemodynamic instability
* Additional serum hCG level

STUDY ASSESSMENTS – DAY 14 (IF 2ND VINORELBINE DOSE ADMINISTERED)

* Perform clinical examination to assess for signs of evolving tubular rupture or haemodynamic instability, or other compromise
* Serum hCG
* FBE, U&Es and LFTs
* Repeat U/S (if indicated)

PHONE CALL FOLLOW UP

* Regular post-treatment phone calls to assess for participants’ return to menses, the participant’s assessment of the acceptability of vinorelbine therapy (including treatment side effects, admission and follow up requirements) and subsequent fertility, pregnancy and/or birth data will be made by the researchers for 2 years.
  1. **SAFETY ASSESSMENTS**

All participants will be admitted to NSH for the initial phases of their treatment and for several hours following the administration of their vinorelbine doses. Within NSH, there is 24 hour specialist medical and nursing (including gynaecology, surgical, anaesthetic and critical care staff) available in case of a serious medical event or allergic reaction.

As a part of the routine management for women with ectopic pregnancies, participants will undergo frequent, multimodal monitoring until their pregnancy is resolved. This management and these test results will be overseen by the participants’ treating clinicians, with additional reviews performed by the research team during the collation of results into the CRF.

Trial participants will have baseline observations performed prior to the administration of the 1st dose of vinorelbine, and will have their wellbeing reassessed (as well as an assessment for any adverse events) within 3 hours of taking the 1st dose.

Trial participants will be closely monitored for the progress or resolution of their ectopic pregnancy; serum hCG levels; and biochemical indices of haematological toxicities, hepatic and renal impairment before, during and after their treatment course of vinorelbine.

Participants will have the 24 hour phone number to the on call emergency gynaecology doctor at NSH, in case of a clinical deterioration after their discharge from hospital.

Following any AE involving a participant, an obstetrician/gynaecologist who is also a member of the research team will review the patient and the history of the AE to establish severity and causality of the event (see *Section 10*), determining whether or not the event was likely attributed to vinorelbine. They will also arrange for any necessary follow up with the patient in an attempt to ensure that the AE is resolved satisfactorily.

* 1. **SUMMARY TABLE OF STUDY ASSESSMENTS**

### TABLE 2: Summary of study assessments

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Day 1**  **(day of 1st treatment), prior to dose administration** | **Day 1, following 1st dose** | **Day 4** | **Day 7, prior to 2nd dose** | **Day 11**  **(only if required)** | **Day 14**  **(only if 2nd dose given)** | **Follow up phone calls** |
| **Consent** | ✔ | ✔\* | ✔\* | ✔\* | ✔\* | ✔\* | ✔\* |
| **Medical history review** | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |  |
| **Check path results: hCG/FBE/LFT/ U&E/ Ultrasounds** | ✔ |  | ✔ | ✔\*\* | ✔\*\* | ✔\*\* |  |
| **Clinical examination** | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |  |
| **Assess for adverse events** |  | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| **IMP regime compliance** |  | ✔ |  | ✔ |  |  |  |
| **Assess for return to menses; subsequent fertility, pregnancy and birth outcomes** |  |  |  |  |  |  | ✔ |

**\* = Verbally confirm ongoing consent**

**\*\* = Continue monitoring results until ectopic pregnancy resolved**

* 1. **LONG TERM FOLLOW UP ASSESSMENTS**

At the time of application, the researchers intend to make phone contact on a few occasions with the participants in the months following their course of vinorelbine. These follow up calls will give the researchers the opportunity to gain information regarding participants’ return to normal menses and subsequent fertility, pregnancy and birth outcomes.

* 1. **STORAGE AND ANALYSIS OF SAMPLES**

The EPC clinicians will retain responsibility for organising the collection of all routine pathology tests that area a part of the normal medical management of a stable ectopic pregnancy. The on-site researchers at NSH will have responsibility for organising for any supplementary or study-specific tests to be added in to the participants’ management plans.

All non-routine blood samples (the Day 4 FBE/U&Es/LFTs, as outlined in *Sections 3* and *7*) taken for this study will be analysed by the NSH’s local contracted pathology provider along with the concurrent routine hCG test. The handling and analysis of the additional Day 4 blood tests will be paid for out of project funds. These samples will be handled, analysed and disposed by the pathology provider’s staff in accordance with their local policies and guidelines. The research team will access the participants’ pathology results and transpose the data into the Case Report Form (CRF).

1. **DATA COLLECTION**

The participants’ medical records and pathology results are considered to be source data. Information will be transcribed or copied (with abridgments, where appropriate) into the CRF. Data will be collected and transcribed as it becomes available, at each point of contact that the research team has with the participant. It is anticipated that with a small sample size and multiple Co-Investigators/Associate Researchers, participant follow-up will be well-attended and missing data will be kept to a minimum. Where possible, data will be collected from patients regardless of their compliance with the treatment regime (see *Section 9.2.3*). Study protocol compliance will be commented on in the study analysis. The researchers will attempt to collect and report on reasons for any missing data or deviations from study medication regime.

1. **STATISTICS AND DATA ANALYSIS**
   1. **SAMPLE SIZE CALCULATION/RATIONALE**

The researchers plan to recruit 20 women with stable ectopic pregnancies over a period of 12-18 months. The researchers believe that this sample size is justified as follows:

* Many ‘first in man’ studies recruit 10 to 20 participants. Whilst vinorelbine is already prescribed for other treatment indications, it has not yet been administered to an exclusive cohort of women with ectopic pregnancies
* 20 is a modest number, however it will be sufficient to obtain drug safety, toxicity and tolerability information and give preliminary data about vinorelbine’s capacity to treat the disease mechanisms of ectopic pregnancy
* A recent phase II clinical trial published in *BMJ Open* [13] investigated the efficacy and side effect profiles of combination methotrexate and gefitinib therapy for the medical management of stable ectopic pregnancies with a sample size of 28 participants
* A recent case report published in the American Journal of Obstetrics and Gynaecology [14] examined the pharmacokinetic profile and effects of pravastatin on preeclampsia in a sample size of 20 pregnant participants
* The researchers are targeting those women who present with stable ectopic pregnancies who have no other contraindications to medical management of their condition. Considering that around 75% of ectopic pregnancies are currently managed surgically [1, 6], 20 participants is a realistic number that can be recruited for medical management with vinorelbine over 18 months, when accounting for those cases who will inevitably decline inclusion or will be otherwise excluded from participating.
  1. **PROPOSED ANALYSES**

Statistical analysis for this study will be performed using *GraphPad Prism 6* (GraphPad Software, La Jolla, CA). Given the study design and objectives of this particular trial:

1. There is no comparison arm, so clinical variables and the clinical course will be presented as descriptive statistics
2. There is no power calculation to perform
3. Continuous variables will be statistically analysed using a t-test (parametric) or a Mann-Whitney test (non-parametric), as appropriate
4. Categorical variables will be statistically analysed using a chi-squared test or Fisher’s exact test, as appropriate
5. Biochemical pathology results will be assessed as continuous variables
6. A p value of <0.05 will be considered statistically significant.
   * 1. **Primary outcome analysis**
7. The primary objective of this study is to assess the safety, toxicity and tolerability of administering vinorelbine to patients with ectopic pregnancies
8. We will assess and monitor for adverse effects and sensitivity reactions of vinorelbine in the participants (e.g. anaphylaxis; gastrointestinal upset; dyspnoea)
9. We will assess participants’ biochemistry to monitor for possible toxic side effects of vinorelbine (e.g. granulocytopaenia)
10. We will measure the tolerability/acceptability of the treatment regime to the participants via questionnaires during the follow-up phone consultations.
    * 1. **Secondary outcome analyses**
11. The secondary objective will be to determine the effects of vinorelbine on clinical and biochemical markers of ectopic pregnancy resolution (or progression).
12. We will assess the efficacy of vinorelbine in resolving ectopic pregnancies (compared to a contemporaneous cohort who receive standard methotrexate therapy) by looking at the occurrence of clinical symptoms of a non-resolving ectopic pregnancy (e.g. subsequent tubular rupture); occurrence of ‘failed medical management’ progressing to salvage surgery; and the progression/regression of biochemical aspects of the disease (including serial serum hCG levels; liver function, renal function and haematological parameters).
13. Furthermore, we will assess the participants’ return to menses and subsequent pregnancy and birth data over a two-year period to gather data on the impact of vinorelbine on human fertility
    * 1. **Missing data/sensitivity analyses**

Missing data will be presented descriptively.

* + 1. **Subgroup analyses**

This study will not be powered to perform subgroup analyses.

* + 1. **Interim analysis**

An interim analysis will not be conducted for this study.

* + 1. **Final analysis**

A final analysis will be conducted by the trial Investigators.

1. **ADVERSE EVENTS**

Medsafe’s Information for Health Professionals (see *Appendix 1*) for Navelbine® (vinorelbine) contains the full details of the known contraindications and side effects that have been reported following the administration.

Participants who are recruited to the trial will be instructed to inform their direct clinical care team or a member of the research team at any time during their participation if they develop symptoms, whether or not they think these may be related to vinorelbine. All AEs that occur after consenting to the trial must be logged in detail in the CRF or recorded in an AE log. In the case of an AE which may be related to the administration of the Investigational Medical Product (IMP), a medically-qualified Investigator will initiate any appropriate treatment(s), according to their clinical judgement.

The Site Leader is responsible for the detection, documentation and follow-up of events experienced by participants during their enrolment in the study that meet the criteria and definitions as detailed below.

* 1. **DEFINITIONS**

This trial will be undertaken with the approval of the HDEC and Maori Research and Ethics Committee. Adverse events will be managed according to the following definitions, recommendations and requirements, guided by ICH-GCP principles, Medsafe GCP guidelines [15] and the National Health and Medical Research Council (NHMRC)’s *National Statement* [16].

An **Adverse Event**(AE) is any untoward medical occurrence in a study participant who has been administered an IMP. An AE *does not necessarily have a causal relationship* with the IMP in question.

An **Adverse Drug Reaction**(ADR) is any unintended, noxious response to an IMP at any dose, where a causal relationship between the IMP and the reaction *cannot be ruled out*.

A **Serious Adverse Event** (SAE) or **Serious Adverse Drug Reaction**(SADR) is defined as any AE or ADR that:

* Results in the death of a participant;
* Is life-threatening (puts the participant at risk of death of the time of the event – it does not refer to an event which could have hypothetically ended in death, had the event been more severe);
* Requires inpatient hospitalisation, or prolongation/escalation of existing hospitalisation;
* Results in a congenital abnormality or birth defect; or
* Results in significant or persistent incapacity/disability

An **Unexpected Adverse Drug Reaction** (UADR) is an ADR, the nature or severity of which is not consistent with the available manufacturer’s Product Information (*Appendix 1).*

A **Suspected, Unexpected, Serious Adverse Reaction** (SUSAR) is any ADR that is:

* Classified as serious;
* Suspected to be caused by the IMP; and
* Not consistent with the information available in the manufacturer’s Product Information
  1. **IDENTIFYING AEs AND SAEs**

All AEs/SAEs will be recorded from the time a participant signs the consent form until their follow up phone calls have been completed. Any AE must be recorded on the AE log page in the CRF. Admission to hospital will not be considered as an AE/SAE, if it follows the course of normal clinical management for this cohort. An escalation of hospitalisation (e.g. from general ward to intensive care) as a result of taking the IMP (e.g. an anaphylactic reaction) will be classified as a SAE/SADR. A tubular rupture or subsequent surgical management required by the participants will be noted as a SAE and not as a SADR, as it follows the normal disease progression following the failed medical management of an ectopic pregnancy.

Participants will be asked about the occurrence of AEs/SAEs at every research team contact episode during the treatment phase of the study, using open-ended and non-leading questions (e.g. “Tell me about how you’ve been feeling”), as well as specific questions relating to any occurrence of common ADRs (e.g. gastrointestinal symptoms). Known, common gastrointestinal side effects of vinorelbine (nausea, vomiting, diarrhoea, constipation) will be noted on the CRF but do not need to be recorded as AEs, unless meeting the criteria for a ‘serious’ or ‘severe’ event (see *Section 10.1*).

Participants’ medication charts will be reviewed to assess for study protocol compliance, as well as to monitor concomitant medications. AEs/SAEs may also be identified via information from the medical history or other source documents (e.g. abnormal pathology test results not consistent with the woman’s ectopic pregnancy resolving). If there is any doubt whether or not an event or clinical observation constitutes an AE, the event will be recorded as an AE.

* 1. **RECORDING AEs AND SAEs**

Following notification of the occurrence of an AE or SAE, it is the responsibility of the Site Leader to review all documentation and source data related to the incident, as well as recording and reporting the event to the relevant body/bodies (i.e. the Co-ordinating Trials Office, HDEC, Medsafe, etc.). The Site Leader must record all relevant information in the CRF and complete a SAE form, if the event meets the criteria of a ‘serious’ incident (as outlined in *Section 10.1*). Required information includes:

* Date of event onset
* Type of event
* Temporality
* Medication dosages
* Assessment of causality and severity
* Treatments/investigations required
* Time to resolution
* Incident outcome

These responsibilities may be delegated by the Site Leader to another suitably qualified medical doctor who is also a registered Investigator associated with the study (these responsibilities must be documented on the delegation log).

* 1. **ASSESSMENT OF AEs AND SAEs**

A medically-qualified Investigator must assess all AEs/ADRs as they occur for their seriousness, expectedness, causality and severity. As this is a single arm study, all AEs will be assessed knowing that the participant is taking the Investigational Medical Product (IMP). Any event that is classified as ‘Serious’ (SAE/SADR/SUSAR) must be notified to the Site Leader within 24 hours of a Co-Investigator’s first awareness of the event.

The Site Leader or designated medical Co-Investigator will review all AEs that are reported to them by members of the study team as being ‘Serious’. The Site Leader may not downgrade an event that has been assessed by another Investigator as ‘serious’ (SAE, SADR or SUSAR), but they may upgrade a reported AE/ADR to a ‘serious event’ as they deem appropriate. The Site Leader must also organise (or delegate appropriately) to inform the HDEC, TSC and DSMC of any new information or research that comes to light during the trial regarding the safety of the drug which could impact on the ethical acceptability of the study’s continuation.

* + 1. **Assessment of seriousness**

A medically-qualified Investigator who is named on the delegation log will make an assessment of any reported event’s seriousness (as defined in *Section 10.1)*.

* + 1. **Assessment of causality**

A medically-qualified Investigator will make an assessment of the likelihood of an AE/SAE being related to the IMP according to these definitions:

* ‘Unrelated’: Where an event is assessed as being not causally related to the administration of the IMP
* ‘Possibly related’: The AE is assessed as being possibly causally related to the IMP (based on the nature of the event, temporal relationship between AE and IMP dosing, concomitant medications, or the underlying medical condition).

This assessment of causality will be referenced against the safety information detailed in *Appendix 1*. The Investigator may further sub-classify this assessment as ‘unlikely, but possibly related’, or ‘likely to be related’, according to their assessment of the event

*Note:* If an AE is considered to be attributed to the interaction between the IMP *and* another concomitant medication - or where an AE could be linked to *either*the IMP or a concomitant medication - the AE must be categorised as an ADR of vinorelbine.

* + 1. **Assessment of expectedness**

If an event is classified as an ADR, the assessing Investigator must use the information in the manufacturer’s Product Information to assign a level of expectedness to the ADR, based on existing knowledge of the drug’s potential to cause that particular event. The ADR must be termed as either:

* ‘Expected’: The ADR is consistent with the known toxicity profile of the IMP, as outlined in *Appendix 1*; or
* ‘Unexpected’: The ADR is not consistent with the known toxicity profile of the IMP
  + 1. **Assessment of severity**

The assessing Investigator will assign one of the three following categories of severity for each AE/SAE, and record their findings on the CRF/AE form:

* ‘Mild’: An AE that is easily tolerated by the participant, causing minimal discomfort and does not interfere with normal, daily activities
* ‘Moderate’: An AE that causes sufficient discomfort and interferes with the participant’s normal, daily activities
* ‘Severe’: An AE that prevents the participants from being able to perform their normal daily activities

*Note:* ‘Severity’ and ‘seriousness’ should not be confused – a severity rating is used to describe the intensity of an event, while seriousness is a regulatory definition based on participant or event outcome (see *Section 10.1*). One AE might be serious but not severe (e.g. Grade 1 neutropaenia), while another could be severe but not serious (e.g. nausea).

* 1. **REPORTING OF SAEs/SADRs/SUSARs**

Once an investigator becomes aware that a study participant has experienced a SAE/SADR/SUSAR, the information will be immediately reported to the NSH Site Leader and co-ordinating trials office, no later than 24 hours after the assessing Investigator’s first awareness of the event.

If an Investigator does not have detailed or complete information regarding the SAE/SADR/SUSAR, they should not delay informing the Site Leader about the event – once additional information is received, the SAE report form can be updated. The first submission of a SAE report form will outline an assessment of seriousness, causality, expectedness and severity (see *Sections 10.4.1-* *10.4.4*) at the time of the initial report being made to the PI.

SAE report forms can be submitted by hand to the co-ordinating trials office; transmitted by fax or sent in PDF format by email to pchowdary@waitematadhb.govt.nz (PI); and [stong@unimelb.edu.au](mailto:stong@unimelb.edu.au) (PI). If a report is being submitted outside of business hours, phone contact must also be made with the on-call Site Leader. Where missing information is not subsequently sent through to the Site Leader/PIs following an initial report, the relevant investigator will be contacted to follow up and obtain additional information. All SAE reports and follow up information will be retained and compiled by the relevant Site Leader (or designee) in the *Investigator Site File* (ISF).

The PIs will organise onward reporting to HDEC and other regulatory authorities (as appropriate) following any SAE/SADR/SUSAR experienced by a study participant during this trial, as outlined in *Sections 10.6*, *10.7* and *Appendix 2*.

* 1. **REGULATORY REPORTING REQUIREMENTS**

As outlined in *Section 10.5*, Clinical Investigators must also inform the PIs within 24 hours of their first knowledge of any Adverse Events (AEs) that meet the criteria as being either ‘serious’ (as defined in *Sections 10.1* and *10.2*) and/or ‘unexpected’ (as outlined in *Sections 10.1* and *10.4.3*). The Site Leader will organise for the timely reporting of any relevant events to HDEC or the appropriate regulatory bodies, as required by HDEC’s conditional approval of the study and other relevant Medsafe guidelines.

Other AEs/ADRs should be reported by the Co-Investigators in the CRF and forwarded to the Site Leader and PI in a timely manner. The Site Leader will inform HDEC of any events that meet the reporting requirements in their conditional approval of the study, or in accordance with relevant Medsafe guidelines.

When a suspected adverse drug reaction (ADR) to a Medsafe-registered medication occurs, the details of the event must be reported to the Centre for Adverse Reactions Monitoring (CARM). Notifications can be made by filling out an online form (available from <https://nzphvc.otago.ac.nz/report/>). Hard copy ADR report forms (see *Appendix 2*) can be sent by fax or mail to CARM, by following the directions outlined by Medsafe on <http://www.medsafe.govt.nz/Profs/adverse/reactions.asp>.

* 1. **FOLLOW UP PROCEDURES**

After recording an AE on the CRF (or recording and reporting a SAE), the event will be followed by the research team until a final outcome can be recorded. This may include follow up visits, assessments or other contact with the affected participant that are supplementary to the course of normal clinical care or the normal study protocol.

If a resolution to an event cannot be established by the Investigators, an explanation of the efforts made to do so will be recorded in the CRF or AE log; or as an addition to the SAE reporting form submitted to the PIs.

Follow-up information from any SAEs will be reported as updates to the initial report form and submitted by the PIs within regulatory timeframes to HDEC, the Sponsor or relevant regulatory authorities (as appropriate).

1. **PREGNANCY AND BREASTFEEDING**

Vinorelbine is a Category D drug (see *Appendix 1*) and has been shown to cause harm to the developing fetus in animal studies. There is no specific data regarding its safety during pregnancy in human studies. Participants will be advised to avoid subsequent pregnancies for three months following their last vinorelbine dose. This is consistent with the advice given to women following treatment for ectopic pregnancies with methotrexate (Category X), another chemotherapeutic drug. Any women who become pregnant again within this window should receive counselling about the potential risks to the developing fetus from an appropriately-qualified and registered genetic counsellor, doctor or midwife who has the capacity to refer the woman to any other clinician or health care service that may be appropriate to her situation and wishes.

There is no data pertaining to the excretion of vinorelbine into human breastmilk. The research team is therefore taking the conservative approach of excluding women who are breastfeeding from participating in this study.

1. **TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS**
   1. **TRIAL STEERING COMMITTEE**

The Trial Steering Committee (TSC) is made up of the study’s Principal Investigators:

* Prathima Chowdary – Principal Investigator and Site Leader at North Shore Hospital; Consultant Endosurgical Gynaecologist
* Stephen Tong - Head of the University of Melbourne Translational Obstetrics Group/Co-director of Mercy Perinatal/Consultant Obstetrician

The TSC is responsible for the protocol creation; the conduct and direction of the study in accordance with ICH-GCP principles and the HDEC-approved study protocol; analysis of study data; oversight of the recruitment and treatment of trial participants; supervision of and delegation of roles to Co-Investigators; and communicating with the HDECs, Medsafe and the Data and Safety Monitoring Committee. Representatives TSC will meet before the commencement of recruitment and thereafter on a 6-monthly basis throughout the conduct of the trial (or more frequently, as required).

* 1. **DATA AND SAFETY MONITORING COMMITTEE**

The Data and Safety Monitoring Committee (DSMC) will provide independent supervision for the trial. The DSMC will provide advice to the Sponsor, Investigational Site, TSC and other Associate Researchers on all aspects of the trial, as well as providing protection for the participants by ensuring that the study is being run in accordance with ICH-GCP and local ethical guidelines and legal requirements. The DSMC will specifically monitor for ongoing safety of trial participants, as well as the scientific validity and merit of the trial. The DSMC will meet on a 6-monthly basis with representative(s) of the TSC throughout the conduct of the trial (or more frequently, as required).

* 1. **INSPECTION OF RECORDS**

All study Investigators (and other relevant employees) associated with the NSH and the University of Melbourne will permit trial-related monitoring and audits to be undertaken by the DSMC; the TSC; HDECs; Maori Research Ethics and any regulatory authority inspections. In the case of an audit, trial monitoring activity, or regulatory inspection, all Investigators involved with the study agree to allow the inspectors and representatives of the Sponsor/HDEC direct access to all study records and source data. This may include facilitating appropriate access to medical histories through the Investigational Site’s Health Information Services department. The potential for participants’ medical records to be accessed by approved persons conducting audit and safety-related inspections of the conduct of the study will form a part of the informed consent process and will be outlined in the PICF.

* 1. **RISK ASSESSMENT**

Specific interim risk assessments (encompassing clinical outcomes and AE examinations for women involved in the study) will be performed by the Trial Steering Committee and Data and Safety Monitoring Committee at meetings held every 6 months throughout the trial. These risk assessments will be performed to establish the need of any mid-trial study design adaptations and to provide information regarding the ongoing safety and ethical acceptability of the trial.

A summative risk assessment at the completion of the trial will help to inform one of the primary outcomes of the study – the safety profile of vinorelbine in women with ectopic pregnancies (see *Section 2.1.1*). The outcomes of each risk assessment will form the basis of subsequent trial monitoring and audit plans. The assessments will also provide information to researchers about specific features to incorporate into future study designs to mitigate risks to participants. HDEC will be informed of the outcome of each risk assessment (with the next scheduled annual HDEC update, if no major findings are made).

* 1. **STUDY MONITORING AND AUDIT**

The PIs or other designated representatives of the TSC will perform study monitoring activities in accordance with the trial monitoring plan (see *Section 12.6*). This will involve investigational site visits and central monitoring activities, as appropriate. Study audits will be performed by members of the TSC in accordance with the study audit plan, including investigator site, study documentation, study management and facility audits as necessary. The DSMC, HDEC and other regulatory bodies may also elect to undertake quality management or quality assurance activities to ensure the safe and ethical conduct of the trial and adherence to the study protocol.

* 1. **TRIAL MONITORING PLAN**

Study monitoring will be conducted at the Investigational Site (NSH) during the trial for quality monitoring and assurance purposes. Member(s) or representative(s) of the TSC will perform audit activities at each site within 3 months of the commencement of recruitment, and every 6 months thereafter, for the duration of the data collection component of the study. Audit activities may include (but are not limited to) the inspection of consent forms to ensure appropriate completion; comparison of CRFs to source documents to ensure accuracy of transposed data; and discussions with Investigational Site staff regarding the conduct of the trial. Audit and monitoring results will be reported to HDEC and the sponsor immediately if major breaches or issues are detected; otherwise with routine HDEC updates that are scheduled to occur annually.

1. **GOOD CLINICAL PRACTICE**
   1. **ETHICAL CONDUCT**

This study has been planned and will be implemented and conducted in accordance with ICH-GCP, TGA, Medsafe, EMA and NHMRC guidelines. The Researchers involved with this trial all hold current GCP certification; are currently undergoing GCP training; or work under the close supervision of a GCP-certified fellow Investigator. The study will commence once approval by the HDEC and the Maori Research Ethics Committee has been obtained and any conditions of approval have been met.

* 1. **REQUIRED APPROVALS AND CONDITIONS OF APPROVAL**

Prior to study commencement, approval has been/will be obtained for conducting the trial from the ANZCTR; HDEC; Maori Research Ethics Committee; Medsafe; the University of Melbourne; and the appropriate senior executive staff at NSH. Any conditions of approval will be met prior to the commencement of the study.

* 1. **REGULATORY COMPLIANCE**

The protocol and study conduct will comply with Medsafe’s *Clinical trials – Regulatory approval and Good Clinical Practice* document (ref) and the NHMRC’s *National Statement* [16]. No specific regulatory approval or oversight from SCOTT is required for this study, as vinorelbine is not a new medication and is already approved for use in New Zealand for other indications.

* 1. **INVESTIGATOR RESPONSIBILITIES**

The PI/NSH Site Leader retains overall responsibility of the conduct of the trial at the Investigational Site; compliance with the study protocol; and the supervision of other researchers. Protocol amendments must involve the PIs, TSC, DMSC, HDEC, Maori Research and Ethics Commttiee and other associated research staff (as appropriate). In accordance with ICH-GCP principles, the PI who is located on-site at NSH is also responsible for the study components as described in *Sections 13.4.1-13.4.8*; however these responsibilities may be delegated to other appropriately-qualified researchers. Dissemination of these responsibilities will be appropriately documented in the delegation log.

* + 1. **Informed consent**

An Investigator who has had their association with this trial acknowledged by HDEC will approach women who are identified as eligible, potential participants to have an initial discussion about the trial, and to provide the appropriate, HDEC-approved PICF. The (potential) participants must be made aware that their decision to take part in clinical research is completely voluntary in nature, and should be based on a clear and accurate understanding of what is involved, the potential risks and possible benefits of their participation. Any women who ultimately consent to the trial will retain their copy of the PICF for their personal records.

Participants must receive adequate oral and written information about the study before being asked to provide their written, informed consent. The oral explanation must address all of the key elements outlined in the PICF. Given that this trial involves the use of an investigational chemotherapeutic medication, a PI or Co-Investigator who is also a qualified O&G consultant or trainee, is ultimately responsible for obtaining written, informed consent from each participant prior to the commencement of any protocol-specific procedures or treatments. When a Co-Investigator who is not a qualified O&G doctor has also contributed to the consenting process, their involvement will be appropriately documented on the CRF and the consent form.

Every opportunity must be given to the participants to ask questions; clarify any information that they do not understand; consult with any chosen and appropriate family members/friends/treating clinicians/community elders/advisors/Maori Health Workers; and seek any additional answers that they may need. The participant must be given sufficient time to consider and reflect upon the information provided. It should be emphasised that the participant may withdraw their consent at any point in time without compromising their access to clinical care, their relationship with the clinical care team, or North Shore Hospital.

As a part of the consenting process, participants must be informed and agree to their medical records (potentially) being reviewed by relevant authorities or Sponsor personnel for regulatory inspection, trial monitoring and trial audit purposes. It should be made clear to the participant that their name and other personal details will not be disclosed outside of their treating hospital.

The Investigator(s) involved in the consenting process and the participant must each personally sign and date the informed consent sheet to confirm that participant’s consent has been appropriately obtained. The signing of the consent form is a formal declaration by each party of their belief that the participant has a clear and accurate understanding of the trial; its purpose; what is involved; the potential risks and possible benefits; and with this knowledge, is readily volunteering for the study. The participant will be given a copy of their signed consent form for their personal records. Another copy will be filed in the participant’s medical history, and another copy will be stored in the ISF.

* + 1. **Study site staff**

All of the study Investigators must be familiar with the IMP (vinorelbine), study protocol, inclusion/exclusion criteria and the study requirements. It is the Site Leader’s responsibility to ensure that all staff involved with the study have a clear understanding of the study protocol, their trial related duties, and the IMP.

* + 1. **Data recording**

The PI is responsible for the quality of the data recorded in the CRF at their Investigational Site. All relevant data captured by the CRFs will be transferred into a username and password-protected database (using REDCap software, administered by University of Melbourne) by delegated Investigators, with the approval of the PIs.

* + 1. **Investigator documentation**

Before commencing work on the study, each member of the research team will be required to provide particular essential documentation to the PIs and HDEC (as appropriate) to establish their credentials and suitability for the role. This documentation may include but is not limited to:

* A summarised Curriculum Vitae
* A signed ‘Investigator’s Declaration’ form
* Evidence of ICH-GCP training/certification (if applicable)

The PIs will ensure that all Investigator documents required by ICH-GCP guidelines are retained in a Trial Master File (TMF)/ISF. The PIs may delegate responsibility for the TMF to another appropriate researcher – this must be documented in the trial delegation log.

* + 1. **GCP training**

All staff involved with the study must have undergone recent ICH-GCP training and hold current ICH-GCP certification of a level appropriate to their role; or be working under the close supervision of an Investigator who has.

* + 1. **Confidentiality**

All staff involved with the study must comply with the treating hospital’s local SOPs and protocols pertaining to confidentiality when undertaking work relating to this study. Additionally, to protect the confidentiality of trial participants and research staff members, the following steps will be taken:

* All participants will be allocated a unique study code, once informed consent has been obtained
* All source data transcriptions or copies, laboratory specimens, CRF entries, evaluation forms, reports and other records will be de-identified of participants’ personal information and marked with their unique study code
* All participants’ study records and research staff information (e.g. CVs) will be kept in secure computer, work or storage areas with limited access
* Clinical information will not be shared with anyone outside of the research team or the participant’s direct clinical carers, without the written permission of the participant (with the exception of any regulatory audit or quality management requirements)
  + 1. **Intellectual Property**

Members of the research team will have a level of access to raw data, analysed data, study results, research records, and other unpublished and confidential information relating to this study through the course of their work. Without the express agreement of the PIs, no unpublished or confidential data obtained for this study may be:

* Used in any other capacity
* Used for any other research projects
* Disclosed to any third parties (with the exception of regulatory compliance activities)
* Published or presented in any capacity
  + 1. **Data protection**

All members of the research team, investigational site staff and organisations involved in this study must comply with the requirements for the handling of participants’ personal information set out in their local hospital’s SOP, New Zealand’s *Privacy Act 1993* and (where relevant) Australia’s *Privacy Act 1988*. Care must be taken to protect the personal information and identities of participants with specific regard to the collection, storage, disclosure and processing of health information gained during the course of this medical research.

Access to collated participant data will be restricted to relevant members of the research team; those clinicians involved in the direct clinical care of the participants in question; authorised representatives of the Sponsor; and any relevant regulatory authority personnel. In accordance with the *Privacy Act 1993*, any personal information that is sent outside of New Zealand (i.e. to the Sponsor in Australia) must be presented so that the participant(s) are not personally identifiable.

Computers and computer programs used to collect, collate and analyse data will have limited access measures (username and password protection). Any paper copies of data will be kept in secure, lockable filing cabinets in the trial site offices. Following the study, the Investigational Site may elect to organise for the study data to be sent offsite to a secure, long term data storage facility which complies with relevant legislation.

Published results of this study will be in statistical or tabulated form and will not contain any personal information that could lead to the identification of individual participants.

* 1. **POTENTIAL CONFLICT OF INTEREST**

The PI/NSH Site Leader (Prathima Chowdary) will also be working clinically as an endosurgery/gynaecology consultant in the EPC at NSH during the recruitment and treatment phases of this study. Other Co-investigators located at NSH may also work in a clinical capacity in the EPC during this time. The PI and these Co-Investigators may be involved in the delivery of clinical care to study participants, as well as to eligible women who decline inclusion, and to those who are excluded from the trial. NSH’s local guidelines and protocols for the treatment of women with ectopic pregnancies will be followed by all clinicians and researchers when making decisions regarding the treatment of EPC patients, regardless of their eligibility and/or enrolment status in this trial.

The Site Leader has undergone ICH-GCP training and holds current certification. The Site Leader will be supervising all Co-Investigators working at NSH. An eligible patient’s decision to either participate or decline inclusion in the study will not impact on their access to the best available medical care at NSH. The wellbeing and best interests of women presenting for care with ectopic pregnancies will remain the paramount consideration of all members of the research and EPC clinical teams. The conduct of this study, its protocol and its staff will be impartially reviewed by HDEC on an ongoing basis throughout this study.

There are no financial conflicts of interest to declare. All funding for the conduct of this study comes from grants courtesy of philanthropic grants and Australian Government sources.

1. **STUDY CONDUCT RESPONSIBILITIES**
   1. **PROTOCOL AMENDMENTS**

Any proposed changes to research activity or study protocol amendments relating to this trial must be reviewed and approved by the TSC and HDEC, with the exception of those changes which are deemed necessary as an urgent safety measure or to remove an apparent threat to the immediate health or safety of a participant.

Proposed amendments to the study protocol must be submitted in writing for approval to the HDEC prior to any participants being enrolled under the amended protocol.

* 1. **PROTOCOL VIOLATIONS AND DEVIATIONS**

Protocol waivers, or prospective protocol deviations, will not be approved for this study (except where it is necessary to eliminate an immediate hazard to study participants). If changes to the study protocol are deemed necessary, they must be proposed as protocol amendments and submitted to HDEC (as outlined in *Section 14.1*) for approval.

Any protocol deviations or violations that do occur will be recorded in a protocol deviation log. Each deviation must be reported to the Site Leader and PI within 24 hours of a researcher becoming aware that the deviation has taken place. The Site Leader and PI must compile the deviation logs and submit them for annual review to HDEC.

* 1. **SERIOUS BREACH REQUIREMENTS**

A ‘serious breach’ is a protocol violation that is likely to cause a significant threat to either:

* The physical or mental health, safety or wellbeing of one or more trial participant(s); or
* The scientific merit, validity, conduct, or ethical acceptability of the trial

If any member of the research team becomes aware of a potential or suspected serious breach occurring, they must notify the on-call PI *within 24 hours of their discovery of the information*. It is the responsibility of the PIs; other members of the Trial Steering Committee; and/or Data and Safety Monitoring Committee (as appropriate) to determine whether or not the event constitutes a ‘serious breach’; to assess the potential or real impact of the breach on the validity of the trial or safety of participants; and to decide whether immediate reporting of the incident to HDEC and/or any regulatory authorities may be warranted.

* 1. **STUDY RECORD RETENTION**

In accordance with New Zealand’s *Health (Retention of Health Information) Regulations 1996*, records created in relation to this research project will be kept for a minimum of 10 years following the end of the study data collection phase (as defined in *Section 14.5*). The Investigational Site, TSC or Sponsor may elect to outsource the safekeeping of records to a secure, off-site storage facility. Once the minimum retention period has lapsed, permission will be sought from senior representatives of the Sponsor before any records are permitted to be shredded (hard copies) or deleted (electronic copies).

* 1. **END OF STUDY**

The ‘end of study’ for this trial is defined as the last point of direct patient contact between the research team and the participants for data collection purposes. This would likely be the date of the two year post-treatment follow-up phone call made to the final remaining participant in the study. However, the TSC, DSMC and/or the Sponsor have the right to terminate the trial at any time prior to this point for clinical safety or administrative reasons. The date of a premature trial termination would then constitute the ‘end of study’ date.

The end of study date will be reported to HDEC within 90 days of completion; or within 15 days if the trial is terminated prematurely. The Site Leader will inform participants in the instance of a premature study closure and ensure that any appropriate follow up is arranged for all participants involved.

A summary report of the study will be disseminated within 1 year of the completion of the trial, as described in *Section 15.2*.

* 1. **CONTINUATION OF DRUG FOLLOWING THE END OF THE STUDY**

Not applicable – IMP administration will be ceased following the second dose, or upon a participant’s withdrawal from the study.

* 1. **INSURANCE AND INDEMNITY**

The Sponsor (the University of Melbourne Department) and Investigational Site (North Shore Hospital, Auckland) are responsible for ensuring that proper provisions have been made for insurance and indemnity to cover their own liability, as well as that of the Principal Investigators, Associate Investigators and the other members of the research team relating to their work on this study.

The Investigational Site will retain their normal duty of care responsibilities towards participants of the study as patients receiving treatment at their health service. The Investigational Site will be liable for any clinical negligence or other forms of negligent harm inflicted upon participants through their health service. The Sponsor of this study requires the Investigational Site to have their own insurance arrangements in place relating to these responsibilities.

The following arrangements are in place to fulfil the Sponsor’s obligations for the provision of indemnity cover relating to the conduct of this trial:

* This study will be conducted at the Waitemata District Health Board’s North Shore Hospital in accordance with the conditional approval being sought from the HDEC. No trial-specific activities will commence until HDEC approval has been granted and any specified conditions of said approval have been met.
* Women of Maori and Pasifika heritage form an integral part of the community all over New Zealand, including in the Waitemata District Health Board Catchment area. As such, the researchers may approach Maori or Pasifika women who are eligible for this trial to discuss potential participation with them. To ensure that the specific cultural sensitivities and needs of women in these communities are met, this project will also seek input, consultation and approval from Maori Research Ethics Committee prior to the commencement of the study. The researchers acknowledge the vital contribution that Maori women may make to this project and in turn, have aimed to design this project in a way that will equitably share any potential health benefits discovered during the course of this research with the Maori and Pasifika communities. All Maori and Pasifika women who are considering enrolling in this study will have the opportunity to discuss the trial, medication, outcomes, follow-up and any specific cultural considerations with a Maori Health Liaison before being asked to provide their consent to participate.
* This study has been registered with the ANZCTR (registration number ACTRN-1261-7001-1183-92p).
* The study protocol has been designed by Principal Investigator Prathima Chowdary; Associate Investigator Roxanne Hastie; and Associate Investigator Anna Middleton with the approval of Principal Investigator (Stephen Tong) and the University of Melbourne Head of Department of Obstetrics and Gynaecology (Susan Walker). The study protocol will be approved by independent peer review, the Trial Steering Committee, the Data and Safety Monitoring Committee and the New Zealand HDEC prior to the commencement of the trial.
* Section 32 in Part 2 of New Zealand’s *Accident Compensation Act 2001* outlines that indemnity cover for investigators and appropriate compensation for ‘treatment injuries’ incurred by a participant or participants in a clinical trial being conducted in New Zealand will be provided by the Accident Compensation Corporation, provided that the following conditions are met:
  + - Approval for the conduct of the clinical trial in New Zealand has been provided by an HDEC
    - The HDEC is satisfied that the trial is not being conducted principally for the benefit of the manufacturer or distributer of the medication being investigated
    - The HDEC providing approval for the study had been granted the authority to operate as an ethics committee by the Health Research Council of New Zealand or the Director-General of Health at the time that study approval was granted

This trial will not commence until final approval has been granted by the HDEC. Additionally, no funding has been sought from, offered by, or received from a drug manufacturer or distributer – this investigator-initiated trial is being funded by philanthropic and Australian Government research grants (as outlined in *Section 13.5*).

* A formal Clinical Research Trial Agreement Contract for this collaborative trial is being created with the assistance of the University of Melbourne Legal Department to formalise the arrangements for the conduct of this study between the University of Melbourne, North Shore Hospital and Mercy Perinatal. The contract will be approved and counter-signed by senior representatives of the Trial Steering Committee, NSH and the University of Melbourne prior to the commencement of recruitment.
* As the Investigational Medical Product (vinorelbine) is already approved for use in New Zealand for the treatment of other conditions, this trial does not require approval from New Zealand’s *Standing Committee on Therapeutic Trials* (SCOTT).

1. **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**
   1. **AUTHORSHIP POLICY**

Ownership of all data arising from this study remains with the members of the study team. Upon completion of the data collection component of the study, the data will be analysed (as outlined in *Section 9*), with an ICH-GCP-compliant clinical study report prepared.

* 1. **PUBLICATION**

The clinical study report will be submitted to the approving HDEC, Maori Research Ethics Committee, the contributing funding bodies (NHMRC and Mercy Foundation) and relevant regulatory authorities within one year of the study’s completion. A copy will also be forwarded to senior representatives of the Sponsor and the Investigational Site.

The study report will be used by approved members of the research team to present the results of the trial at scientific meetings. The PIs will have the right to submit or to grant permission for the submission of the results of the study for written and/or oral publication.

A summary of the study results will be made available to the other members of the research team, who may, at their discretion, disseminate the findings within their clinics. A lay summary of the results will be made publically available by the Sponsor and Investigational Site, in accordance with ICH-GCP recommendations. Given that this is a small study, a lay summary may also be sent directly to the individual participants of the study, at the discretion of the Site Leader.

* 1. **PEER REVIEW**

This trial, its scientific merit and protocol document have been extensively reviewed by clinician-scientist Dr Fiona Brownfoot (Consultant Obstetrician and Gynaecologist; Maternal and Fetal Medicine Fellow; PhD) and clinician Dr Julie Lamont (Consultant Gynaecological Oncologist) prior to the submission of this study to HDEC and the commencement of study recruitment.

# APPENDIX 1: Medsafe - New Zealand Medicines and Medical Devices Safety Authourity – Information for Healthcare Professionals: Navelbine® oral (vinorelbine 20 mg and 30 mg soft capsules)

*Retrieved from:* <http://www.medsafe.govt.nz/profs/datasheet/n/Navelbinecap.htm>

**Information for Healthcare Professionals**

Revised: 17 June 2015

**Data Sheet**

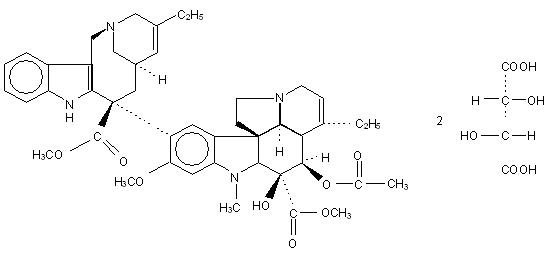
**NAVELBINE® ORAL**

**Vinorelbine 20 mg and 30 mg soft capsules.**

**Description**

Vinorelbine tartrate is a semi-synthetic vinca alkaloid with antitumor activity. The chemical name is 3',4'-didehydro-4'-deoxy-C'-norvincaleukoblastine [ *R-(R\*,R\*)* -2,3 dihydroxybutanedioate (1:2)(salt)].

Vinorelbine tartrate has the following structure:



CAS No: 125317-39-7

Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular formula C45H54N4O8.2C4H6O6 and molecular weight of 1079.12. The aqueous solubility is > 1000 mg/mL in distilled water.

NAVELBINE® soft capsules also contains the following excipients: ethanol, water - purified, glycerol, macrogol 400, gelatin, sorbitol, sorbitan, medium-chain triglycerides, phosphatidyl choline, glycerides, hypromellose, propylene glycol, edible printing ink E120, titanium dixoide, iron oxide yellow CI77492 and / or iron oxide red CI77491.

**Pharmacology**

Vinorelbine is an antineoplastic drug. It is a semi-synthetic member of the vinca alkaloid family that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of two multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. In intact tectal plates from mouse embryos, vinorelbine, vincristine, and vinblastine inhibited mitotic microtubule formation at the same concentration (2µM), including a blockade of cells at metaphase. Vincristine produced depolymerisation of axonal tubules at 5µM, but vinblastine and vinorelbine did not have this effect until concentrations of 30µM and 40µM respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

**Pharmacokinetics**

Following oral administration, NAVELBINE® is promptly absorbed and the Tmax is reached within 1.5 to 3 hours with a blood concentration peak (Cmax) of approximately 130 ng/mL after dosing at 80 mg/m². The absolute bioavailability is about 40% and simultaneous intake of a low fat standard meal does not modify the area-under the concentration-time curve (AUC). The effect of a high fat meal on absorption has not been studied.

NAVELBINE® Oral 60 and 80 mg/m² leads to a comparable AUC to that obtained from 25 and 30 mg/m² of the IV formulation respectively. Interindividual variability of the AUC is similar after administration by both the IV and oral routes. There is a proportional increase between the AUC and dose. The mean pharmacokinetic parameters were evaluated in blood. After intravenous administration, the terminal half-life averaged 38 hours. Blood clearance was high, approached liver blood flow and averaged 0.72 L/hr/kg (range: 0.32 - 1.26 L/hr/kg), while steady state volume of distribution was large, averaged 21.2 L/kg (range: 7.5 - 39.7 L/kg), and indicated extensive tissue distribution.

Vinorelbine binds extensively to blood cells and especially platelets (70-80%), but less extansively (about 15%) to plasma proteins. There is a significant uptake of NAVELBINE® in lungs, as assessed by pulmonary surgical biopsies showing up to a 300 fold greater concentration than in serum. NAVELBINE® has not been detected in the central nervous system.

NAVELBINE® is mostly metabolised by the CYP 3A4 isoform of the cytochrome P450. All the metabolites have been identified, and none are active except 4-O-deacetylvinorelbine, which is the main metabolite in blood. No sulfo or glucurono conjugates are observed. Renal elimination is low (<20% of the dose) and consists mostly of the parent compound. Biliary excretion is the predominant elimination route of both metabolites and unchanged NAVELBINE®, which is the main recovered compound. The effect of renal dysfunction on NAVELBINE® disposition has not been assessed, however dose reduction in the presence of renal insufficiency is not indicated with NAVELBINE® due to its low renal elimination.

Vinorelbine is cleared from the circulation primarily by the liver, and therefore elevated blood concentrations may be expected in patients with hepatic impairment. In a Phase I pharmacokinetic study, 6 subjects with severe hepatic impairment were treated with 20 mg/m² intravenously. Plasma concentrations were elevated compared to historical data from patients with normal hepatic function. Vinorelbine is contraindicated in patients with severe hepatic insufficiency. There is limited experience in patients with mild or moderate hepatic impairment, however available data suggests that dose modification is not required. Haematological toxicity should be closely monitored.

A strong relationship was demonstrated between AUC and leucocyte or PMN decreases.

**Clinical Trials:**

**NAVELBINE® IV:**

**Advanced breast cancer**

**Non-small cell lung cancer**The activity of vinorelbine was investigated in a series of phase II trials. The overall response rate to vinorelbine single agent in NSCLC patients ranged from 8% to 33% in previously untreated patients. In the two major phase II trials with more than 60 evaluable patients, the overall response rate was over 30% in chemotherapy-naive patients. The high activity of vinorelbine as single agent in non-small cell lung cancer which was observed in non-controlled phase II studies has also been confirmed in three randomised phase III trials. In one prospective randomised study with 216 stage IV patients, vinorelbine was compared to 5-fluorouracil with leucovorin (considered equivalent to best supportive care for the purposes of the study). The median survival time of patients who received vinorelbine was 30 weeks compared to 22 weeks for those on the 5-fluorouracil/leucovorin arm (log-rank p=0.03). The response rates were 12% for the vinorelbine arm and 3% for the fluorouracil/leucovorin arm.

The activity of vinorelbine in combination with cisplatin has been investigated in two randomised phase III trials in a total of 782 patients. In a two arm trial, vinorelbine was compared to vinorelbine with cisplatin. The overall response rate to vinorelbine as single agent was 16% while that of the combination vinorelbine/cisplatin was 43%. The median survival time for patients receiving vinorelbine as single agent was similar to that observed with vinorelbine and cisplatin.

In a large European clinical trial, 612 patients with Stage III or IV non-small cell lung cancer, no prior chemotherapy and WHO performance Status of 0, 1 or 2 were randomised to treatment with single-agent vinorelbine (30 mg/m²/week), vinorelbine (30 mg/m²/week) cisplatin (120 mg/m² days 1 and 29 then every 6 weeks), and vindesine (3 mg/m²/week for 7 weeks, then every second week) plus cisplatin (120 mg/m² days 1 and 29 then every 6 weeks). Vinorelbine plus cisplatin produced longer survival times than vindesine plus cisplatin (median survival 40 weeks vs 32 weeks, p=0.03). The median survival time for patients receiving single-agent vinorelbine was similar to that observed with vindesine plus cisplatin (31 weeks vs 32 weeks). The 1-year survival rates were 36% for vinorelbine plus cisplatin, 27% for vindesine plus cisplatin, and 30% for single-agent vinorelbine. The overall objective response rate (all partial responses) was significantly higher in patients treated with vinorelbine plus cisplatin (28%) than in those treated with vindesine plus cisplatin (19%, p=0.03) and in those treated with single-agent vinorelbine (14%, p<0.001). The response rates reported for vindesine plus cisplatin and single-agent vinorelbine were not significantly different. Significantly, less nausea, vomiting, alopecia, and neurotoxicity were observed in patients receiving single-agent vinorelbine compared to those receiving the combination of vindesine and cisplatin.

**NAVELBINE® Oral**

Oral vinorelbine has been developed as a line extension of the IV dosage form. Hence the primary objective of the clinical program was to demonstrate bioequivalence between the oral and intravenous formulations on the basis of pharmacokinetic studies. An oral dose of 80 mg/m² was demonstrated to correspond to 30 mg/m² of the IV formulation and 60 mg/m² orally to 25 mg/m² given by the IV route.

Subsequent phase II studies, were conducted to examine the efficacy and tolerance of oral vinorelbine

**Non-small cell lung cancer**One randomised Phase II study with the recommended oral dose regimen was conducted, comparing oral and IV vinorelbine in patients with advanced or metastatic NSCLC who had not been previously treated with cytotoxic chemotherapy. Results are summarised in thefollowing table:

|  | **Oral vinorelbine** | **IV vinorelbine** |
| --- | --- | --- |
| **Study I - CA 205** |  |  |
| No of subjects | 77 | 38 |
| Response rate (ITT population) | 11.7% | 10.5% |
| Response rate (Evaluable population) | 14.1% | 11.8% |
| Median duration of response | 7.7 months | 5.5 months |
| Median progression-free survival | 3.3 months | 2.1 months |
| Median Survival | 9.4 months | 7.9 months |

In a multicentre, phase II study of 56 patients in combination with cisplatin 100 mg/m² (day 1 q 4 weeks), the weekly administration of vinorelbine (IV vinorelbine 25 mg/m² day 1, oral vinorelbine 60 mg/m² days 8, 15 and 22) produced a response rate of 30% for all registered patients and 33% for evaluable patients in the first line treatment of unresectable, localised or metastatic NSCLC. Median progression-free survival and survival were 5.5 and 8.9 months, respectively.

**Indications**

NAVELBINE® is indicated as a single agent or in combination for the treatment of non small cell lung cancer (NSCLC).

**Contraindications**

Known hypersensitivity to vinorelbine or other vinca alkaloids.

Disease significantly affecting absorption.

Previous significant surgical resection of stomach or small bowel.

Neutrophil counts < 1500 cells/mm³, or current or recent severe infection due to neutropenia (within 2 weeks).

Pregnancy.

Lactation.

Patients requiring long-term oxygen therapy.

Severe hepatic insufficiency.

**Precautions**

**Administration**

NAVELBINE® soft capsule should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. If the patient chews or sucks the capsule by mistake, rinse mouth with water or preferably a normal saline solution.

In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the physician in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.

If vomiting occurs within a few hours of drug intake, administration of the dose should not be repeated. Prophylactic treatment with metoclopramide or oral antiemetics may reduce the incidence. It is recommended that the capsule be taken with food.

**Myelosuppression**

Neutropenia is dose-limiting. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of NAVELBINE®. Patients treated with NAVELBINE® should be frequently monitored for myelosuppression both during and after therapy. NAVELBINE® should not be administered to patients with neutrophil counts < 1500 cells/mm³.

Patients developing severe neutropenia should be monitored carefully for evidence of infection and/or fever. If patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out. (See DOSAGE AND ADMINISTRATION for recommended dose adjustments for neutropenia).

NAVELBINE® should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy (see DOSAGE AND ADMINISTRATION).

During clinical trials where treatment was initiated at a weekly dose of 80 mg/m² (corresponding to an IV dose of 30 mg/m² in terms of systemic exposure), febrile neutropenia, in some cases fatal, was encountered in about 15% of patients. Therefore, it is recommended that the starting dose should be 60 mg/m² and increased to 80 mg/m² only if the dose is tolerated (see DOSAGE AND ADMINISTRATION).Laboratory tests

Since dose-limiting clinical toxicity is the result of depression of the white blood cell count, it is imperative that complete blood counts with differentials be obtained and reviewed on the day of treatment prior to each dose of NAVELBINE®. If the neutrophil count is below 1500 / mm³ and/or the platelet count is between 75,000 and 100,000 / mm³, then treatment should be delayed until recovery.

**General**

Most drug-related adverse events of NAVELBINE® are reversible. If severe adverse events occur, NAVELBINE® should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with NAVELBINE® should be carried out with caution and alertness as to possible recurrence of toxicity.

Patients presenting with ischaemic cardiac disease should be carefully monitored (see ADVERSE REACTIONS).

Acute shortness of breath and severe bronchospasm have been reported infrequently along with rare cases of interstitial pneumopathy following the administration of NAVELBINE® and other vinca alkaloids, most commonly when the vinca alkaloid was used in combination with mitomycin. These adverse events may require treatment with supplemental oxygen, bronchodilators, and/or corticosteroids, particularly when there is a pre-existing pulmonary dysfunction.

Vinorelbine is contraindicated in patients with severe hepatic insufficiency. There is limited experience in patients with mild or moderate hepatic impairment, however available data suggest that dose modification is not required. Haematological toxicity should be closely monitored.NAVELBINE® should not be given concomitantly with radiotherapy if the treatment field includes the liver.

Because of the low level of renal excretion, no dose modification is necessary in patients with renal impairment.

Due to the presence of sorbitol, patients with the rare hereditary problem of fructose intolerance should not take this medicine

**Carcinogenicity/Mutagenicity**

Vinorelbine tartrate has been shown to affect chromosome number and possibly structure in vivo (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice).

It was not mutagenic or cytotoxic in a reverse histidine mutation (Ames) test but showed mutagenic potential in a mouse forward mutation (TK locus) test. Carcinogenicity studies in mice and rats showed no tumourigenic activity at dose levels up to 2.4 mg/m² given by IV injection every two weeks for 18 months or two years respectively. However, the positive findings in genetic toxicity assays suggest that the drug may have carcinogenic potential at the higher dose level used in humans.

**Effects on fertility**

Adverse effects on the male reproductive system were observed in repeat-dose toxicity studies in animals, including decreased spermatogenesis in rats dosed twice weekly at 2.1 - 7.2 mg/m² for 13 weeks, reduced prostate/seminal vesicle secretion in rats dosed twice weekly at 3 mg/m² for 26 weeks, reduced testicular weight in mice dosed at 19 mg/m²/day for three 5-day cycles, and reduced epididymal weight in dogs dosed at 5 mg/m² for 26 weeks. Vinorelbine tartrate did not affect fertility when administered to male and female rats prior to and during mating; however, the doses used in these studies (9 mg/m² once weekly or up to 4.2 mg/m² at 3-day intervals) were lower than the human dose.

**Use in pregnancy**

**Category D**  
NAVELBINE® may cause fetal harm if administered to a pregnant woman. When given every three days during organogenesis, vinorelbine tartrate has been shown to be teratogenic in rats and rabbits at doses of 3 and 7.7 mg/m² respectively. A single 9 mg/m² dose of vinorelbine tartrate caused embryonic deaths in mice. Doses causing adverse fetal effects in animals were lower than the human dose. There are no studies in pregnant women. If NAVELBINE® is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with NAVELBINE®.

**Use in lactation**

It is not known whether vinorelbine is excreted in milk of animals or humans. A study in rats showed that growth of the offspring was suppressed when vinorelbine tartrate was administered to lactating dams at 6 mg/m² every three days. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from NAVELBINE®, it is recommended that nursing be discontinued in women who are receiving therapy with NAVELBINE®.

**Interaction with other drugs**

Acute pulmonary reactions have been reported with NAVELBINE® and other vinca alkaloids used in conjunction with mitomycin. NAVELBINE® should be administered with caution in combination with mitomycin.

The combination of NAVELBINE® soft capsules and other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

In the absence of specific studies evaluating drug-drug interaction with warfarin, the patient should be cautiously monitored when vinorelbine is given in combination with warfarin.

Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of toxicities, specifically granulocytopenia, with the combination of NAVELBINE® and cisplatin is significantly higher than with single-agent NAVELBINE®.

In studies with rats, the anticoagulant effect of phenindione was potentiated when given in combination with high dose of vinorelbine (30 mg/m²/day for 4 consecutive days or 15 mg/m²/day for 5 consecutive days) but combination treatment with sodium valproate did not cause any increase in anticonvulsant activity.

Vinorelbine is metabolised by cytochrome CYP3A4. Although interaction studies have not been performed, it is expected that inhibitors of CYP3A4 such as ketoconazole, itraconazole, ritinovir etc, would result in elevated blood concentrations of vinorelbine. Inducers of CYP3A4 such as rifampicin and phenytoin may reduce concentrations of vinorelbine. Since the magnitude of the inducing or inhibiting effects is unknown, such drug combinations should be avoided.

**Food**

Simultaneous intake of a low fat standard meal does not modify exposure to vinorelbine.

**Paediatric use**

Safety and effectiveness have not been established.

**Geriatric Use**

Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Adverse Reactions**

The reported incidence of undesirable effects with NAVELBINE® Oral was determined from clinical studies in 210 patients.

**Haematological**

Neutropenia is the dose-limiting toxicity with NAVELBINE®. Neutropenia (Grade 1-2:

24%, Grade 3: 19%, Grade 4: 23.8%) was rapidly reversible and non-cumulative. Grade 4 neutropenia was associated with a fever over 38°C in 2.9% of patients. Further treatment may be given after recovery of the neutrophil count. Infections were observed in 15.2% of patients but were severe in 5.2%.

Anaemia was very common but usually mild to moderate (Grade 3: 4.3%, Grade 4: 0.5%). Thrombocytopenia may also occur but was seldom severe (Grade 1 to 2: 12.9%). Dose adjustments are required for haematologic toxicity (see DOSAGE AND ADMINISTRATION).

**Neurological**

Neurosensory disorders were generally limited to loss of deep tendon reflexes (Grades 1 to 2: 12.4%) and infrequently severe. One patient presented partially reversible grade 3 ataxia. Neuromotor disorders were seen in 10.0% of patients (Grade 3: 1.0%).

Neuroconstipation was seen in 11.3% of patients (Grades 1 to 2: 10%) and rarely progressed to paralytic ileus (1.4%). One episode of fatal paralytic ileus was reported. Use of prescription laxatives may be appropriate in patients with prior history of constipation and/or who received concomitant treatment with opioid analgesics.

Mild to moderate peripheral neuropathy manifested by paraesthesia and loss of deep tendon reflexes (Grade 3: 2.5%, Grade 4: 0.2%) and hyperesthesia have been reported with IV administration. After prolonged treatment, weakness of the lower extremities has also been reported. The effects are dose dependent but usually reversible when treatment is discontinued.

**Gastrointestinal**

Gastrointestinal adverse events occur more commonly with oral vinorelbine than with intravenous administration. Gastrointestinal adverse events reported included: nausea (Grades 1 to 2: 70.5%, Grade 3: 8.6%, Grade 4: 0.5%), vomiting (Grades 1 to 2: 52.9%, Grade 3: 4.3%, Grade 4: 3.3%), diarrhoea (Grades 1 to 2: 41.9%, Grade 3: 2.9%, Grade 4: 2.4%), and anorexia (Grades 1 to 2: 26.7%, Grade 3: 4.8%, Grade 4: 1.0%). Concomitant supportive treatment with metoclopramide or 5HT3 antagonists may reduce the occurrence of nausea and vomiting.

Stomatitis usually mild to moderate occurred (Grades 1-2: 8.7%). Oesophagitis was seen in 4.8% of patients (Grade 3: 0.5%). Pancreatitis has been reported very rarely when vinorelbine is given intravenously.

**Other**

Fatigue (Grades 1-2: 19.5%, Grade 3: 6.7%), fever (Grades 1-2: 12.4%), arthralgia including jaw pain, myalgia (Grades 1-2: 9.0%), pain including pain at the tumour site (Grades 1-2: 5.2%) have been experienced by patients receiving NAVELBINE® Oral. Haemorrhagic cystitis and the syndrome of inappropriate ADH secretions were each reported in < 1% of patients given Navelbine® IV. Rare cases of severe hyponatraemia have been reported with Navelbine® IV.

In addition, it cannot be ruled out that the following effects may also be experienced with use of NAVELBINE® Oral, as they have been observed with intravenous administration, and with other vinca alkaloids.

**Cardiovascular**

There have been rare reports of ischemic cardiac disease (angina pectoris, myocardial infarction). In very rare cases, cardiac failure and pulmonary oedema have been reported during treatment with Navelbine® IV, however a causal relationship has not been established.

**Hepatic**

Transient elevations of liver enzymes were reported without clinical symptoms.

**Respiratory**

As with other vinca alkaloids, the intravenous administration of NAVELBINE® has been associated with dyspnea, bronchospasm and rare cases of interstitial pneumopathy in particular in patients treated with NAVELBINE® in combination with mitomycin.

**Dermatological**

Alopecia is usually mild (Grades 1-2: 27.1%) and may appear progressively with extended courses of treatment. Rarely vinca alkaloids may produce generalised cutaneous reactions.

**Adverse Reactions from post-marketing surveillance**

Frequencies are defined as: *very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000).*

| **System organ class (MedDRA classification)** | **Very common (>10%)** | **Common (>1% and ≤10%)** | **Uncommon (>0.1% and ≤1%)** |
| --- | --- | --- | --- |
| **Blood and lymphatic system disorders** | Neutropenia (grades 1 to 4) Anaemia (grades 1 to 4) Thrombocytopenia (grades 1 to 2) | Anaemia (grade 3) | Anaemia (grade 4) |
| **Gastrointestinal disorders** | Nausea (grades 1 to 2) Vomiting (grades 1 to 2) Diarrhoea (grades 1 to 2) Anorexia (grades 1 to 2) | Nausea (grade 3) Vomiting (grades 3 to 4) Stomatitis (grades 1 to 2) Diarrhoea (grades 3 to 4) Oesophagitis (grades 1 to 2) Anorexia (grade 3) | Nausea (grade 4) Oesophagitis (grade 3) Anorexia (grade 4) |
| **Peripheral autonomic and central nervous system disorders** | Loss of Tendon reflexes (grades 1 to 2) | Neuromotor disorders (grades 1 to 2) Neuro-comstipation (grades 1 to 2) Paralytic ileus | Neuromotor disorders (grade 3) Ataxia (grade 3) |
| **Skin and subcutaneous tissue disorders** | Alopecia (grades 1 to 2) |  |  |
| **General disorders and administration site conditions** | Fatigue (grades 1 to 2) Fever (grades 1 to 2) | Fatigue (grade 3) Pain (grades 1 to 2) |  |
| **Musculoskeletal and connective tissue disorders** |  | Arthralgia (grades 1 to 2) Myalgia (grades 1 to 2) |  |

**Dosage and Administration**

NAVELBINE® soft capsules must be given strictly via the oral route. They should be swallowed whole with water and should not be chewed or sucked. It is recommended that the capsule be taken with food.

**Dosage in adults**

**Single agent**The recommended regimen is:

* **First three administrations:** 60 mg/m², administered once weekly.
* **Subsequent administrations:** Beyond the third administration, it is recommended to increase the dose of NAVELBINE® soft capsules to 80 mg/m² once weekly, except in those patients for whom the neutrophil count has dropped once below <500 / mm³ or more than once between 500 and 1000 / mm³, during the first three administrations at 60 mg/m².

**Dose modifications according to haematological status**

If the neutrophil count is below 1500 / mm³ and/or the platelet count is between 75,000 and 100,000 / mm³, then treatment should be delayed until recovery.

| **Neutrophil count during the first 3 administrations at 60 mg/m²/week** | **Neutrophils >1000** | **Neutrophils ≥ 500 and < 1000 (1 episode)** | **Neutrophils ≥ 500 and < 1000 (2 episodes)** | **Neutrophils <500** |
| --- | --- | --- | --- | --- |
| **Recommended dose for 4th and subsequent administrations** | **80** | **80** | **60** | **60** |

For any administration planned at the 80 mg/m²/week dose, if the neutrophil count falls below 500 / mm³, the dose must be delayed until recovery and reduced from 80 to 60 mg/m² per week during the 3 subsequent administrations.

| **Neutrophil count beyond the 4th administration at 80 mg/m²/week** | **Neutrophils  >1000** | **Neutrophils ≥ 500 and < 1000 (1 episode)** | **Neutrophils ≥ 500 and < 1000 (2 episodes)** | **Neutrophils <500** |
| --- | --- | --- | --- | --- |
| **Recommended dose for the next administration** | **80** | | **60** | |

It is possible to re-escalate the dose from 60 to 80 mg/m²/week if the neutrophil count does not drop below 500/mm³, or more than once between 500 and 1000 / mm³, during the three administrations given at the 60 mg/m² dose.

**Dose modifications for hepatic insufficiency**

Vinorelbine is contraindicated in patients with severe hepatic insufficiency. There is limited experience in patients with mild or moderate hepatic impairment, however available data suggests that dose modification is not required. Haematological toxicity should be closely monitored.

**Combination chemotherapy**

The use of oral vinorelbine in combination regimens has not been extensively studied. However, based on pharmacokinetic studies, the oral dose of 80 mg/m² was demonstrated to correspond to 30 mg/m² of the IV form and 60 mg/m² orally to 25 mg/m² IV.

In combination regimens, intravenous vinorelbine dosing may be replaced with oral vinorelbine therapy. The recommended dose is 60 mg/m². The safety of higher doses of oral vinorelbine (eg 80 mg/m²) in combination regimens has not been established.

The following table gives the dose required for appropriate ranges of body surface area (BSA).

|  | **60 mg/m²** | **80 mg/m²** |
| --- | --- | --- |
| **BSA (m²)** | **Dose (mg)** | **Dose (mg)** |
| 0.95 to 1 | 60 | 80 |
| 1.05 to 1.14 | 70 | 90 |
| 1.15 to 1.24 | 70 | 100 |
| 1.25 to 1.34 | 80 | 100 |
| 1.35 to 1.44 | 80 | 110 |
| 1.45 to 1.54 | 90 | 120 |
| 1.55 to 1.64 | 100 | 130 |
| 1.65 to 1.74 | 100 | 140 |
| 1.75 to 1.84 | 110 | 140 |
| 1.85 to 1.94 | 110 | 150 |
| ≥ 1.95 | 120 | 160 |

Even patients with a body surface area (BSA) ≥ 2 m² the dose should never exceed 120 mg per week at 60 mg/m² and 160 mg per week at 80 mg/m².

Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.

**Overdose**

There is no known antidote for overdoses of NAVELBINE®. No case of overdosage has been reported with NAVELBINE® oral, however the primary anticipated complications of overdosage would consist of bone marrow suppression and peripheral neurotoxicity. If overdosage occurs, general supportive measures together with appropriate blood transfusions and antibiotics should be instituted as deemed necessary by the physician.

**Presentation**

20 mg soft capsule: light brown soft capsule printed N20,

30 mg soft capsule: pink soft capsule printed N30,

Pack size: 1 capsule

**Shelf life**

Store at 2 to 8° C (Refrigerate. Do not freeze) in the original container.

Protect from light.

**Medicine Classification**

Prescription Medicine

**Name and Address**

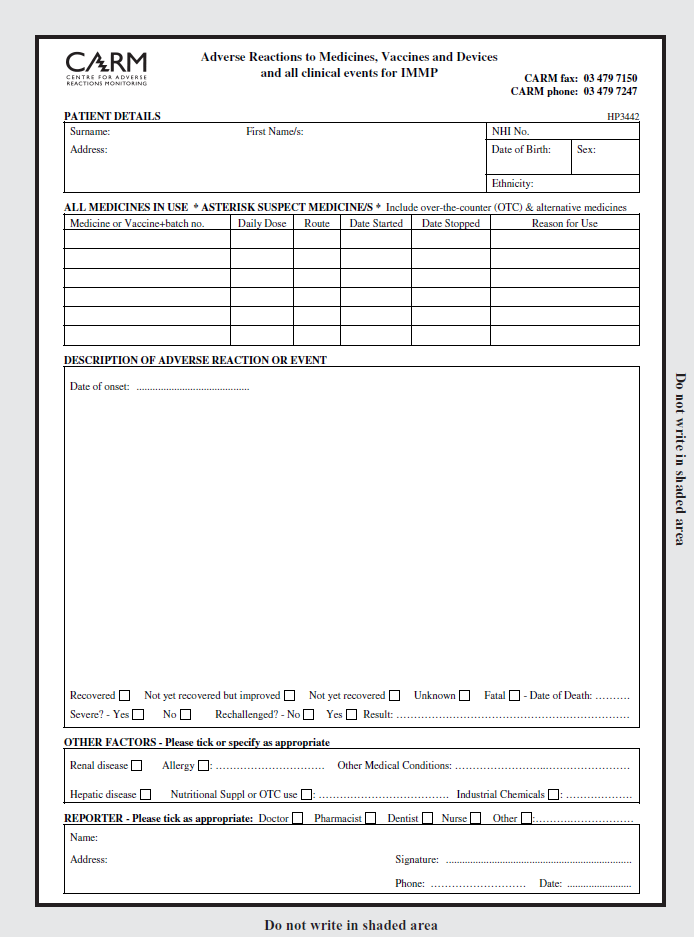
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**Date of Preparation**

6 November 2006

# APPENDIX 2: Centre for Adverse Reactions Monitoring – Adverse reaction reporting form

**From Medsafe’s adverse medication reactions reporting algorithm – retrieved from:** [**http://www.medsafe.govt.nz/Profs/adverse/reactions.asp**](http://www.medsafe.govt.nz/Profs/adverse/reactions.asp)



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