STUDY PROTOCOL

RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF
PYRIDOXINE FOR PREVENTION OF CAPECITABINE INDUCED
HAND-FOOT SYNDROME

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1. STUDY SYNOPSIS

Background
Capecitabine chemotherapy is frequently used in the management of colorectal and breast cancers, and hand-foot syndrome (HFS) is a common side-effect. When grade 2 or greater toxicity occurs, dose interruption or reduction is necessary. Pyridoxine (vitamin B6) is often used to treat HFS, but the evidence is limited to retrospective observational studies. The role of pyridoxine in primary prophylaxis of HFS has not been investigated.

Hypothesis
Concomitant pyridoxine with capecitabine reduces the risk of grade ≥2 HFS.

Objectives
The primary objective is to evaluate the incidence of grade ≥2 HFS in patients receiving pyridoxine compared to placebo. The secondary objectives are to compare the time to onset of grade ≥2 HFS (in days) and impact on quality of life (QOL) in the two groups. Exploratory analyses of serum and red cell folate, serum vitamin B12 and gene polymorphisms involved in capecitabine and pyridoxine metabolism will be performed.

Study design
This is a double-blind placebo-controlled study. Patients on capecitabine single-agent chemotherapy (at a dose of at least 1000mg/m² twice daily for 14 days every 3 weeks) will be randomized to receive concomitant pyridoxine or placebo daily for a maximum of 8 cycles of capecitabine. Patients will be stratified according to gender and use in adjuvant/neo-adjuvant versus palliative setting. A total of 296 patients (148 per arm) will be enrolled over a period of at least 2 years.

Patients who develop grade ≥2 HFS will be withdrawn from the study. Institution of daily pyridoxine with or without dose reduction of capecitabine may subsequently occur at the clinician’s discretion.

Study significance
If pyridoxine is proven to be effective in preventing HFS, there will be less dose disruption and reduction, and the efficacy of the treatment may be maintained. Patient’s quality of life will also improve. If the findings from the study are negative, this may lead to a change in clinical practice worldwide and result in cost savings.
2. STUDY AIM AND OBJECTIVES

The aim of the study is to determine if concomitant pyridoxine will prevent Grade 2 or greater severity hand-foot syndrome (HFS) in patients receiving capecitabine.

Primary objective
To evaluate the incidence of grade ≥2 HFS in patients receiving concomitant pyridoxine compared to placebo.

Secondary objectives
1. To determine the time to onset of grade ≥2 HFS
2. To evaluate the quality of life (QOL) changes using EuroQOL (EQ-5D) questionnaires.
3. To study gene polymorphisms of putative relevance to capecitabine and pyridoxine metabolic pathways (especially thymidylate synthase, thymidine phosphorylase, dihydropyrimidine dehydrogenase, cytidine deaminase, carboxylesterase, methyltetrahydrofolate reductase) and correlate serum and red cell folate levels, serum vitamin B12 levels with toxicity.

3. BACKGROUND AND STUDY RATIONALE

Study hypothesis
Upfront pyridoxine with commencement of capecitabine reduces the risk of developing grade 2 or greater HFS.

Background
Colorectal cancer and breast cancer are two of the commonest types of cancer worldwide. In Singapore, colorectal cancer (CRC) is the second commonest cancer among males with an age-standardised rate (ASR) of 40.1 per 100,000 and the second commonest among Chinese women with an ASR of 29.4 per 100,000. Breast cancer is the commonest cancer among women in Singapore, with an ASR of 54.9 per 100,000. Capecitabine (Xeloda), an oral fluoropyrimidine that is converted to 5-fluorouracil (5-FU) by an enzymatic process, has shown efficacy in the treatment of both breast and gastrointestinal cancers.

As first-line therapy for metastatic colorectal cancer, two large phase III trials have shown that capecitabine achieves a superior response rate (RR) and at least equivalent time to disease progression (TTP) and overall survival compared with intravenous (iv) 5-FU/leucovorin (LV). In the adjuvant treatment of colon carcinoma, capecitabine has been shown to be equally effective as bolus 5-FU/LV with less myelosuppression and mucositis. Capecitabine is also being used in combination with irinotecan and oxaliplatin in the metastatic setting.

With respect to metastatic or advanced breast cancer, capecitabine is active as first-line therapy and in pre-treated patients, both as monotherapy and in combination with other drugs.
As the oral route of administration also offers more convenience and patient acceptability compared with iv 5-FU\textsuperscript{11, 12}, capecitabine is rapidly replacing the role of iv 5-FU.

**Rationale for the study**

Although capecitabine has a favourable safety profile with significantly less diarrhoea, stomatitis, nausea, alopecia and grade 3 or 4 neutropaenia compared to 5-FU/LV\textsuperscript{4, 13}, hand-foot syndrome (HFS) is a common complication. The overall incidence of HFS is estimated to be between 53\% to 62\%, with severe cases (≥ Grade 3) in 16\% to 18\% of patients at a dose of 1250mg/m\textsuperscript{2} twice daily for every 14 out of 21 days.\textsuperscript{4, 14} Although it is not a life-threatening complication, it can be disabling in severe cases and affects the treatment course due to the need for dose interruption or reduction once grade 2 or greater HFS occurs. With capecitabine monotherapy, grade 2 or greater HFS occurs in at least two-thirds of patients who develop HFS.\textsuperscript{8, 15, 16} There is less data on the incidence of HFS with capecitabine and oxaliplatin combination therapy, but phase two studies suggest similar or slightly lower incidence of HFS with the slightly lower dose of capecitabine.\textsuperscript{5, 6}

The specific pathophysiologic mechanism of HFS is unclear. The clinical features of HFS are characteristic and evolve in stages. Most patients have their first (92.9\%) or most severe (67.9\%) episode of HFS within the first two cycles of treatment.\textsuperscript{15} Initially, symptoms are very mild with no obvious changes to the hands and feet. Patients may experience a prodrome of about 3 to 5 days, which consists of vague paraesthesias and tingling of the extremities, or painless swelling or erythema (grade 1). If the drug is continued, the syndrome progresses with painful erythema and swelling (grade 2). It may further progress to fissuring, ulceration and desquamation involving the hands and feet, leading to extreme pain when grasping objects or walking (grade 3).\textsuperscript{15} Resolution of HFS occurs upon discontinuation of capecitabine. Histologically, the condition is marked by hyperkeratosis associated with an inflammatory cell infiltrate and an increase in vascularity of the dermis.\textsuperscript{14}

Although interruption of capecitabine with dose reduction is the most important step in the treatment of HFS, other measures are frequently employed.\textsuperscript{15} Mild cases can be treated with topical emollients and wound care. The rationale for using pyridoxine (vitamin B6) in HFS came from the diagnosis of a similarly appearing skin disease in pyridoxine depleted rats.\textsuperscript{17} Pyridoxine is a water-soluble vitamin which is present in foods such as red meat, bananas, beans and cereals. It is involved in amino acid metabolism, and also in carbohydrate and lipid metabolism. In vivo, pyridoxine is converted mainly to pyridoxal 5'-phosphate which is the active coenzyme in a number of metabolic transformations, including the conversion of tryptophan to niacin or serotonin, the breakdown of glycogen to glucose-1-phosphate, the conversion of oxalate to glycine, the synthesis of gamma-aminobutyric acid (GABA) within the central nervous system (CNS) and the synthesis of heme. In adults, pyridoxine deficiency mainly affects the peripheral nerves, skin, mucous membranes and the haemopoietic system.\textsuperscript{18} There are no postulated mechanisms on how the vitamin may reverse the symptoms of HFS, but there are published reports documenting its efficacy. To date, no prospective randomized trials have been performed on the efficacy of pyridoxine in treating or preventing HFS.

Pyridoxine was first used empirically by Vukelja et al, who treated one patient successfully without interrupting 5-FU treatment.\textsuperscript{19} In a subsequent study involving patients with...
metastatic colorectal cancer receiving continuous infusional 5-FU, 16 of 25 patients developed HFS which occurred at a median of 2 months after initial treatment. Five patients were treated with pyridoxine 50mg or 150mg daily while continuing on the same chemotherapy dose. Four of the five patients experienced improvement of HFS from grade 3 to grade 1, and chemotherapy was continued for a median of 6 months, compared to only 2.5 months in patients who did not receive pyridoxine. No adverse effects were reported in those patients taking pyridoxine. In a different study using a weekly regimen of 5-FU and leucovorin, fourteen out of 52 patients developed HFS. Eleven of the patients received pyridoxine 150mg daily without interruption of the chemotherapy and symptoms improved for all of them within one week. Two patients who discontinued the pyridoxine while continuing chemotherapy experienced recurrence of HFS symptoms within 2 weeks.

Laumann et al subsequently performed a retrospective multi-institutional chart review to determine if pyridoxine was effective in ameliorating the symptoms of capecitabine-induced HFS. Patients receiving doses of pyridoxine ≥200mg/day experienced a greater symptomatic improvement in HFS compared to those receiving lower doses. The data from this pilot study suggests that the addition of pyridoxine allows one to administer higher doses of capecitabine without affecting the clinical efficacy of capecitabine. Higher doses of pyridoxine (>200mg daily) may also be of greater clinical benefit. Other advantages of pyridoxine include its relative lack of adverse effects and its affordable cost.

More recently, East Asian patients were reported to have fewer toxicities than US patients in a retrospective analysis of safety data from randomized single-agent fluoropyrimidine clinical trials. Potential factors giving rise to this difference include genetic polymorphisms, as well as differences in dietary folate intake.

**Significance of the Study**

Based on the limited data above, many patients who develop HFS on capecitabine receive pyridoxine in addition to dose interruption or reduction. There are also clinicians who empirically prescribe upfront pyridoxine for patients commencing capecitabine as primary prophylaxis for HFS. Given that the use of capecitabine is set to increase, there is a need for well-designed prospective controlled trials to investigate the role of pyridoxine in both primary and secondary prophylaxis of HFS.

If pyridoxine is proven to be effective in preventing HFS, there will be less dose disruption and reduction, and the efficacy of the treatment may be maintained. Patient’s quality of life will also improve. If the findings from the study are negative, this should lead to a change in clinical practice worldwide and result in cost savings.

4. **PATIENT SELECTION**

4.1 **Inclusion criteria**

- Patients receiving capecitabine for any malignancy, either in the adjuvant/neoadjuvant or palliative setting
- Patients commencing capecitabine at a dose of ≥1000mg/m² twice daily every 2 out of 3 weeks as single-agent chemotherapy.
- Signed informed consent
Male or female patients, age ≥ 18 years

Life expectancy greater than 12 weeks.

(Concomitant radiotherapy, steroids or biological therapy eg trastuzumab, bevacizumab permitted, as long as they do not cause HFS or neuropathy.)

4.2 Exclusion criteria

• Prior capecitabine chemotherapy

• Inability to provide informed consent

• Concomitant administration of drugs that can cause HFS eg docetaxel, liposomal doxorubicin

• Concomitant administration of drugs that can cause neuropathy eg oxaliplatin, taxanes

• Pre-existing neuropathy confounding assessment of HFS

• Consumption of pyridoxine-containing preparations eg multivitamins, Vitamin B complex

• Anticipated inability to follow-up patient for side-effects of chemotherapy

• Other dermatologic condition, that, in the opinion of the physician, may affect the hands or feet or may complicate evaluation during study treatment

• Concurrent or planned use of over-the-counter products that contain urea or lactic acid eg Aqua Care®, Medicated Calamine® lotion (0.3%), Coppertone® Waterproof Ultra Protection Sunblock, Dr. Scholl’s® Smooth Touch deep moisturizing cream, Depicure® So Smooth Cream, Dove® Moisturizing Cream Wash, Cetaphil® Moisturizing Cream

• Known allergy to pyridoxine and its incipients

• Concomitant administration of drugs reported to have drug interactions with pyridoxine (including cycloserine, hydralazine, immunosuppressants, isoniazid, levodopa, oestrogen or oestrogen-containing contraceptives, penicillamine, phenobarbitone, phenytoin, pyrazinamide)

Patients will be asked to report and/or bring all concurrent medications, over-the-counter preparations and topical applications which will be checked by the treating doctor and trial nurses before entering the study. They will also be reminded of the need to avoid these preparations at each visit.

Reasons for non-entry of potentially eligible patients will also be collected in a screening log (appendix 20.5). The screening log may identify factors that steered patients away from the trial, dissuaded physicians or investigators from entering patients into the trial, and will help assess the generalisability of the findings. The log will not contain any details that can identify patients.

5. STUDY DESIGN

Randomized double-blind placebo-controlled study

5.1 Treatment Plan

Patients commencing capecitabine at a dose of at least 1000mg/m² twice daily every 2 out of 3 weeks will be randomized to receive either concomitant pyridoxine (200mg) or placebo once daily orally for 21 days out of each treatment cycle. In the event that the patient cannot start capecitabine together with pyridoxine or placebo immediately after informed consent was obtained, a maximum dose delay of not more than 4 weeks is allowed.
5.2 Study duration

- Until grade $\geq 2$ HFS occurs, or
- Until capecitabine is ceased (due to disease progression, side effects or other reason), or
- For a maximum duration of 8 cycles (approximately 24 weeks).

6. OUTCOMES AND MEASURES

The primary outcome is the first incidence of grade 2 or greater HFS. The severity of HFS will be graded 1 to 3 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 outlined below.

- Grade 0 No HFS
- Grade 1 Minimal skin changes or dermatitis (e.g., erythema) without pain
- Grade 2 Skin changes (e.g., bleeding, blisters, peeling, oedema) or pain not interfering with function
- Grade 3 Ulcerative dermatitis or skin changes with pain interfering with function

The secondary outcome of time to onset of grade 2 or greater HFS will be evaluated in days. QOL will be assessed using EuroQOL EQ-5D questionnaire (attached in appendix). The EQ-5D, a short generic health-related quality of life (HRQOL) questionnaire, can derive preference-based index scores. It is a five-item questionnaire for assessing HRQoL, plus a visual analogue scale (VAS) of overall health status. It was specifically designed with simplicity and cost-utility analysis in mind and has been tested and used in several disease groups. In relation to other preference-based HRQOL instruments, the EQ-5D is relatively short and easy to complete.

7. STUDY PROCEDURES

Clinician review 3-weekly (window period of ± 4 days is allowed) at the beginning of each cycle (earlier if clinically indicated). Compliance with the medication regimen will be assessed by tablet counts at each visit. If grade $\geq 2$ HFS occurs, patient needs to be assessed by clinician within 4 days of onset.

Baseline blood test for genotyping and serum, red cell folate and serum vitamin B12 levels.

Other routine blood tests (such as full blood count, biochemistry) and investigations before commencement of chemotherapy are to be performed as clinically indicated at the discretion of the treating physician.

Phone review by trial nurse weekly (during the weeks patients do not see their clinicians) regarding compliance and HFS symptoms.

Daily HFS symptom record by patient; diary provided.

QOL assessment at baseline, at beginning of cycles 2, 4, 6, 8 and at the end of the study.
8. INTERVENTIONS

8.1 Management of grade ≥2 HFS

Patients who develop HFS of grade 2 or greater severity will be withdrawn from the study. Institution of daily pyridoxine with or without dose reduction of capecitabine may subsequently occur at the clinician’s discretion.

8.2 Management of grade 1 HFS

Patients who develop grade 1 HFS may be treated with topical emollients if deemed necessary by the treating oncologist. Type of emollient, frequency and duration of use need to be fully documented. Dose interruption or reduction for grade 1 HFS is not permitted.

8.3 Chemotherapy dose modification, delay or interruption for other toxicities

Interruption, delay or modification of dose of capecitabine and/or other cytotoxic drug for other toxicities or reason is permitted. Reason and dose need to be clearly documented.

8.4 Withdrawal criteria

- when Grade 2 or greater HFS occurs or
- if capecitabine is ceased due to disease progression, other side-effects or
- if patient decides to withdraw from the study.
### 9. STUDY CALENDAR

* : Needs to be recorded by clinician at the beginning of the cycle or pre-study or at end of study.

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### 10. GENOTYPING, FOLATE AND VITAMIN B12 LEVELS

Variability in response and toxicity to chemotherapy is determined by genetic factors and also possibly by environmental and physiological factors. Pharmacogenetic studies have identified gene variants that predict for efficacy and toxicity in the treatment of various cancers including CRC. An 8ml sample of blood will be collected from each patient at the same time as routine blood draw using cell preparation tube (CPT) at baseline.
The sample will be identified by the study number with no direct identification of the patient from the sample. DNA will be extracted using standardised methods and stored at minus 20 degree celsius for subsequent genotyping at Dr. Richie Soong’s laboratory. Genotyping for polymorphisms of putative relevance to pyridoxine and capecitabine metabolism (especially thymidylate synthase, thymidine phosphorylase, dihydropyrimidine dehydrogenase, cytidine deaminase, carboxylesterase, methyltetrahydrofolate reductase) will be performed using previously described techniques. Additional 10ml of blood will also be taken for baseline serum and red cell folate and vitamin B12 levels.

The incidence rate of the gene polymorphisms will be summarised and evaluated. Potential associations between gene polymorphisms, folate and vitamin B12 levels and clinical outcome will be performed using appropriate statistical methods.

11. STATISTICAL CONSIDERATIONS AND RANDOMISATION

11.1 Randomization

• Patients are randomized after the eligibility status has been fully determined and an informed consent has been obtained.
• The randomization procedure will be carried out through telephone from the Clinical Trials Office (CTO) of the Division of Clinical Trials & Epidemiological Sciences (CTE), NCC.
• Block randomization will be used. Patients will be stratified according to gender and use in adjuvant/neoadjuvant versus palliative setting. Within each stratum blocks of consecutive patients will be formed. The Block length will be designed by a CTE biostatistician and blinded to all other research personnel until study closure.
• Within each stratum and block, patients will be randomized with equal probability to either:
  - ARM 1: concomitant pyridoxine
  - ARM 2: Placebo (control arm)

11.2 Sample size calculation

The null hypothesis of this study is that concomitant pyridoxine does not reduce the risk of developing grade $\geq 2$ HFS. The alternative hypothesis is that concomitant pyridoxine reduces the risk of grade $\geq 2$ HFS.

The overall incidence of grade $\geq 2$ HFS for capecitabine single-agent cytotoxic therapy is estimated to be 36-40%. Pyridoxine prophylaxis will be clinically worthwhile if it can almost halve the incidence of grade $\geq 2$ HFS.

To detect a reduction in the incidence of HFS from 36% to 20% with upfront pyridoxine at a power of 80%, 123 patients per group will be required. We anticipate that up to 20% of the patients may cease capecitabine before 4 cycles due to reasons such as disease progression and intolerance of other side-effects. To make up for the difficulty in evaluating HFS in these
patients, we intend to recruit extra 20% or 25 patients in each arm. Hence the target accrual will be 296 patients in total with 148 patients for each arm. Interim analysis of results will not be performed.

11.3 Statistical analysis

- Incidence of grade $\geq 2$ HFS (%)
The incidence of grade $\geq 2$ HFS (%) in each arm will be estimated with 95% confidence intervals and will be compared using chi-square test.
Stratification will be performed according to gender and use in adjuvant/neoadjuvant versus palliative setting.

- Time to the onset of grade $\geq 2$ HFS (in days)
Time to the onset of grade $\geq 2$ HFS (in days) will be estimated using the Kaplan-Meier method. Difference in the two arms will be tested by the log-rank test.

- Quality of Life Analysis
The mean EQ-5D index (and standard error) at each time point for each arm will be estimated. Differences between treatment arms in mean EQ-5D index at each time point will be estimated and tested. However, all mean (95% CI) QOL values at each time point and treatment arm will be plotted together and examined graphically. Changes in QOL will be analysed with ANOVA tests.

- Intention-to-treat and per protocol analysis
The intention-to-treat principle will be applied in the main analysis. Per protocol analysis will be used as secondary and sensitivity analysis.

12. ADVERSE EVENTS AND PROTOCOL VIOLATION POLICIES

If there are any adverse events suspected to be related to the treatment drug rather than the cytotoxic drug or other medication or condition, they will be reported (see SAE report form in appendix 21.3).

Protocol violation eg due to non-compliance or lack of follow-up or records, or patient withdrawal as explained previously, will be reported. Patients will still be included in the intent-to-treat analysis.

13. AGENT FORMULATION, DRUG INTERACTIONS, STORAGE AND ACCOUNTABILITY

Pyridoxine is supplied as tablets of 50mg.

Formulation of placebo: tablets matching the pyridoxine tablets in size, colour, appearance and nature of excipients (lactose, cornstarch, plastidon, magnesium stearate).

Source of pyridoxine and placebo supply: Beacons Pharmaceuticals Pte Ltd
Drug interactions: cycloserine, hydralazine, immunosuppressants, isoniazid, levodopa, oestrogen or oestrogen-containing contraceptives, penicillamine, phenobarbitone, phenytoin, pyrazinamide.

Storage (at room temperature) at National Cancer Centre (NCC) Singapore Pharmacy, and these supplies will be accounted for at the site pharmacy.

Please refer to appendix for further information on pyridoxine.

14. LOGISTICAL CONSIDERATIONS

Site(s) to be involved and Study duration
Approximately 1,200 patients are prescribed capecitabine at National Cancer Centre in Singapore annually. Accrual is expected to be about 12 patients per month. 296 patients will be required for this study. Thus, patient accrual is expected to be complete within 2 years. Additional time (approximately 6 months) is required to allow for the final patient entered into the study to receive either pyridoxine or placebo daily for a maximum of 8 cycles of 3-weekly capecitabine chemotherapy.

Other hospitals in Singapore or overseas may also be invited to participate in this trial to accrue patients over a shorter period of time.

Evaluable Patients and Dropouts
All patients registered in the study will be accounted for. Should a patient withdraw from the study without having received the pyridoxine or placebo assigned, then a replacement patient can be registered.

Patients evaluable for efficacy and adverse events are defined as:
- Patients who give informed consent to participate in the trial
- Patients who met all eligibility criteria
- Patients who have received pyridoxine or placebo.

Budget and Potential Funding Sources
The cost of pyridoxine and placebo tablets as well as their storage have been considered. Funding is currently provided by the Singapore Cancer Society Research Grant 2006.

15. ADMINISTRATIVE ASPECTS

Monitoring, Auditing and Inspecting
The study will be monitored at regular intervals. Study procedures and study-related toxicities will be monitored by the principal investigator and any study-related problems will be evaluated and discussed with the investigators.

Patient Identification
All patients screened for the study will have their initials and birth date recorded. If a patient is excluded from the study, the reason is to be documented in a screening log. The investigator will be assigned a block of consecutive patient allocation numbers. Eligible patients entering the study will be assigned a patient allocation number sequentially beginning at the top of the allocation number list. The patient allocation number and patient's initials are to be entered on all case report forms.
Data Handling
Each patient’s data will be kept in individual files (case report forms). Data will be collected by oncology research nurses and data managers. All data, protocols, amendments, authorisations and correspondence will be stored at the trial centre(s). All data will be kept in coded form and information will remain confidential. All data collection will be monitored to ensure thorough and accurate collection.

Recording of Data
Case report forms (CRF) must be typewritten or printed legibly. The forms will be verified against original records (and workbooks, if applicable). CRFs and all original data will be readily available for review.

Record Retention
Copies of all pertinent information will be retained by the investigator for a period of 15 years following the date of study completion.

16. ETHICAL CONSIDERATIONS
Although pyridoxine is frequently used in the treatment or prevention of HFS from capecitabine, the evidence is limited to mainly retrospective observational studies so far. Pyridoxine, being a type of vitamin, rarely causes any side effects at the dosage used in this study. This double-blind placebo-controlled trial will evaluate whether concomitant pyridoxine can significantly prevent grade 2 or greater HFS in patients receiving capecitabine.

Ethical Conduct of the Trial
The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

Centralized Institutional Review Board (CIRB)
It is the responsibility of the investigator to obtain approval of the trial protocol and any amendments of the protocol from the CIRB. The final approved protocol and the patient information sheet and informed consent statement to be administered will be reviewed by the CIRB. The Board's decision concerning conduct of the study will be made in writing to the investigator. All correspondence with the CIRB should be filed by the investigator. The study shall not commence until the CIRB has approved the study.

Patient Information and Consent
It is the responsibility of the investigator to give each patient (or the patient’s acceptable representative) prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The patients must be informed about their right to withdraw from the trial at any time. A CIRB approved written patient information sheet (included as an appendix to the protocol) must be given to each patient before enrolment. An approved informed consent statement will then be read and signed by the patient and the investigator. The written patient information must not be changed without prior approval by the CIRB. Furthermore, it is the responsibility of the investigator to obtain signed informed consent from all patients prior to inclusion in the trial.
The patient will be provided with a copy of the signed informed consent statement. The patient may withdraw from the study at any time without prejudicing future medical treatment. Verification of a signed informed consent statement will be noted on the patient's study CRF.

**Modification of the Protocol**

Any changes to the protocol affecting study objectives, study design, patient population, study procedures or significant administrative aspects will require a formal amendment to the protocol. The CIRB must approve such amendments before being instituted. Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. The CIRB may be notified of administrative changes at the discretion of the investigator.

**Privacy and Confidentiality**

All information obtained as part of the research will remain confidential. Information will be stored securely in coded format and password-protected, but will remain potentially identifiable to investigators only. Information will not be reported to third parties without individual patient consent.

17. **PUBLICATION POLICY**

It is the intention to publish the results of the study based on the final reports produced by the principal investigators. No patients will be identified by name. Results will not be suppressed by the investigators for commercial or other reasons.

18. **INDEMNITY**

There is an indemnity policy for investigator-initiated hospital-based research at National Cancer Centre (NCC), Singapore.


20. APPENDICES

20.1 ECOG performance status grading

<table>
<thead>
<tr>
<th>ECOG</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care but unable to carry out any work; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable only of limited self care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry out any self care; totally confined to bed or chair</td>
</tr>
</tbody>
</table>
20.2 Pyridoxine product information

Pyridoxine Hydrochloride

MIMS Full Prescribing Information
MIMS revision date: 01/05/2002

Composition Active. Pyridoxine hydrochloride.
Inactive. Tablets. Lactose, gelatin, wheat starch, maize starch, propyl hydroxybenzoate, microcrystalline cellulose, calcium stearate.
Injection. Water for injections.

Description
Chemical name: 3-hydroxy-4, 5-bis (hydroxymethyl)-2-picoline hydrochloride. Molecular formula: C8H11NO3.HCl. MW: 205.64. CAS: 58-56-0.
White or almost white crystalline powder, or crystals. Pyridoxine has a slightly bitter, salty taste. Soluble 1 in 5 of water and 1 in 115 of alcohol. Practically insoluble in chloroform and ether.

Actions Pyridoxine, pyridoxal and pyridoxamine are collectively known as the water soluble B6 complex vitamins. Vitamin B6 is involved in amino acid metabolism, and also in carbohydrate and lipid metabolism. In vivo, pyridoxine is converted mainly to pyridoxal 5'-phosphate which is the active coenzyme in a number of metabolic transformations, including the conversion of tryptophan to niacin or serotonin, the breakdown of glycogen to glucose-1-phosphate, the conversion of oxalate to glycine, the synthesis of gamma-aminobutyric acid (GABA) within the central nervous system (CNS) and the synthesis of heme.

The recommended daily intake (RDI) for pyridoxine is dependent on the protein intake, and the Australian RDI is based a requirement of vitamin B6 0.02 mg/g protein. In adults, pyridoxine deficiency mainly affects the peripheral nerves, skin, mucous membranes and the haemopoietic system. In children, the CNS is involved. Single deficiency of pyridoxine is rare, and multiple vitamin deficiency is to be expected in any inadequate diet.

Pharmacokinetics.
Absorption. Pyridoxine, pyridoxal and pyridoxamine are readily absorbed from the gastrointestinal tract, mainly in the jejunum, following oral administration. Normal serum concentrations are 30 to 80 nanogram/mL. Gastrointestinal tract absorption may be diminished in patients with malabsorption syndromes.
Distribution. Vitamin B6 is stored in the liver, however some amounts are stored in the brain and muscle. Pyridoxal and pyridoxal phosphate, the principal forms of the vitamin present in blood, are highly protein bound. Pyridoxal phosphate crosses the placenta and is excreted in breast milk. The plasma concentrations in the fetus are five times greater than in maternal plasma concentrations.
Excretion. Pyridoxine is converted to the active form pyridoxal phosphate. Riboflavin is required for the conversion of pyridoxine phosphate to pyridoxal phosphate. In the liver, pyridoxal phosphate is oxidised to 4-pyridoxic acid and is then excreted in the urine. Pyridoxine has a half-life of approximately 15 to 20 days. Pyridoxine is removed by haemodialysis.

Indications Treatment and prophylaxis of pyridoxine deficiency.
Contraindications Hypersensitivity to pyridoxine.
Precautions Long-term administration of pyridoxine has been associated with the development of peripheral neuropathies. Peripheral neuropathy has generally been associated with doses in excess of 2 g/day for two or more months, but has also been reported with
relatively low doses (50 mg/day). Neuropathic symptoms generally subside after the withdrawal of pyridoxine.

Following the administration of pyridoxine in the treatment of seizures in neonates, severe sedation and respiratory distress have been reported. Therefore, it is recommended that resuscitation facilities be available when pyridoxine is given in these circumstances.

Pyridoxine hydrochloride injections should not be administered to patients receiving levodopa unless a peripheral decarboxylase inhibitor such as carbidopa is also given (see Interactions).

Carcinogenesis, mutagenesis, impairment of fertility. No data are available.

Use in pregnancy. Pyridoxine hydrochloride is a therapeutic good that has been exempted from pregnancy classification.

There are no animal data available on the use of pyridoxine hydrochloride during pregnancy.

Problems in humans have not been documented with the intake of normal daily amounts of pyridoxine. However, the use of large doses during pregnancy has resulted in pyridoxine dependency syndrome in the neonate.

Use in lactation. There are no animal data available on the use of pyridoxine hydrochloride during lactation. Pyridoxine is excreted in breast milk. Problems in the infant have not been documented after the maternal intake of normal daily amounts of pyridoxine. A concentration of pyridoxine in breast milk of approximately 240 nanogram/mL may be expected if the maternal intake of pyridoxine is 2.5 to 5.0 mg/day.

Use in children. Problems in children have not been documented with the intake of normal daily amounts of pyridoxine.

**Interactions**

Cycloserine. Cycloserine may increase the requirement for pyridoxine, and may cause anaemia or peripheral neuritis, by acting as a pyridoxine antagonist or increasing the renal excretion of pyridoxine.

Hydralazine. Hydralazine may increase the requirement for pyridoxine, and may cause anaemia or peripheral neuritis, by acting as a pyridoxine antagonist or increasing the renal excretion of pyridoxine.

Immunosuppressants. Immunosuppressants may increase the requirement for pyridoxine, and may cause anaemia or peripheral neuritis, by acting as pyridoxine antagonists or increasing the renal excretion of pyridoxine.

Isoniazid. Isoniazid may increase the requirement for pyridoxine, and may cause anaemia or peripheral neuritis, by acting as a pyridoxine antagonist or increasing the renal excretion of pyridoxine.

Levodopa. Administration of pyridoxine in doses of 5 mg or greater daily reverses the therapeutic effects of levodopa by accelerating the peripheral metabolism of levodopa. This reversal does not occur if a dopa decarboxylase inhibitor such as carbidopa is also given.

Oestrogen or oestrogen containing oral contraceptives. Administration of these agents may increase the requirements for pyridoxine.

Penicillamine. Penicillamine may increase the requirement for pyridoxine, and may cause anaemia or peripheral neuritis, by acting as a pyridoxine antagonist or increasing the renal excretion of pyridoxine.

Phenobarbitone. Concurrent administration of phenobarbitone and pyridoxine may decrease the serum phenytoin concentration. This effect has been reported with pyridoxine doses of 200 mg or greater daily for one month.

Phenytoin. Concurrent administration of phenytoin and pyridoxine may decrease the serum phenytoin concentration. This effect has been reported with pyridoxine doses of 200 mg or greater daily for one month.
Pyrazinamide. Pyrazinamide may increase the requirement for pyridoxine, and may cause anaemia or peripheral neuritis, by acting as a pyridoxine antagonist or increasing the renal excretion of pyridoxine.

Laboratory tests. Pyridoxine has been reported to produce false positive results in urobilinogen determinations using Ehrlich's reagent.

**Adverse Reactions**

Body as a whole. Allergic reactions have been reported occasionally. Transient dependency symptoms (e.g. nervousness, tremors, abnormal ECG) have been observed upon withdrawal after doses of 200 mg for more than three days.

Central nervous system. Headache, paraesthesia and somnolence have been reported. Sedation and hypotonia have been observed in infants with pyridoxine dependency syndrome treated with pyridoxine. Seizures have occurred after intravenous administration of very large doses of pyridoxine. Prolonged administration of pyridoxine (for two or more months) may cause peripheral sensory neuropathies, progressing from unstable gait and numb feet to numbness and clumsiness of hands. Peripheral neuropathies have generally been associated with long-term doses of 2 g/day or more but may also occur with doses as low as 50 mg/day.

Respiratory system. Dyspnoea and apnoea have been observed in infants with pyridoxine dependency syndrome treated with pyridoxine.

Gastrointestinal. Nausea, abdominal pain, vomiting and loss of appetite have been observed after high doses of pyridoxine.

Skin. Photosensitivity has been reported rarely.

Blood. Decreased serum folic acid, increased serum AST (SGOT).

Other. A transient burning or stinging may occur at the site of injection with intramuscular and subcutaneous administration.

**Dosage and Administration**

Pyridoxine hydrochloride can be administered orally, however when oral administration is not feasible pyridoxine hydrochloride can be administered by injection.

Pyridoxine hydrochloride injection may be administered intravenously, intramuscularly or subcutaneously. There may be temporary burning or stinging pain at the site of subcutaneous or intramuscular injection.

Withdrawal of long-term patients from pyridoxine therapy should be done with gradual dose reduction.

Oral administration. Dosage. The usual dosage is 50 to 150 mg daily in divided doses. As a nutritional supplement, it is usually administered in conjunction with other vitamins of the B group.

Treatment of drug induced deficiency anaemia or neuritis. The usual dose of pyridoxine is 100 to 200 mg daily for three weeks, followed by the prophylactic oral administration of 25 to 100 mg daily.

Parenteral administration. Dosage. The usual dosage is 25 to 200 mg daily or as directed.

Prophylaxis and treatment of pyridoxine deficiency. Pyridoxine may be given as an intravenous infusion as part of total peripheral nutrition. The dose should be individualised according to patient need.

Treatment of drug induced pyridoxine deficiency. The usual dose of pyridoxine is 50 to 200 mg intramuscularly or intravenously per day for 3 weeks, followed by 25 to 100 mg/day as needed.

Treatment of pyridoxine dependency syndrome in adults. Doses of 10 to 600 mg per day intravenously or intramuscularly have been recommended by various sources.

Pyridoxine dependent seizures in infants. An initial dose of 10 to 100 mg intravenously or intramuscularly is recommended, although doses of up to 200 mg intravenously have been used. Severe sedation and respiratory distress have reportedly followed administration of pyridoxine in the treatment of seizures in neonates. It is therefore recommended that resuscitation facilities be available when pyridoxine is given in this setting.
Treatment of isoniazid poisoning. An amount of pyridoxine equal to the amount of isoniazid ingested is recommended. The following dosage regimens have been suggested. An initial dose of 5 g by intravenous infusion over 30 to 60 minutes followed by the remainder of the dose by intravenous infusion over 1 to 2 hours; or an initial dose of 4 to 5 g by intravenous infusion over 30 to 60 minutes followed by an additional 1 g intramuscularly every 30 minutes until the entire dose has been given.

Treatment of cycloserine poisoning. A dose of pyridoxine 300 mg or more per day, given intramuscularly or intravenously, is recommended.

Treatment of hydralazine poisoning. A dose of 25 mg/kg is recommended. One-third of the total dose should be administered intramuscularly, and the remainder is given by intravenous infusion over three hours.

Overdosage Symptoms. The principle effect of pyridoxine overdosage is sensory axonal neuropathy. Central effects have also been described. Neuropathy is most commonly reported after chronic ingestion of 200 to 6,000 mg/day for months or years, but may also occur after a single extremely large parenteral dose. These effects may be delayed by days or weeks following completion of pyridoxine administration. Other symptoms of pyridoxine overdose that have been rarely reported include nystagmus, exacerbation of seizures, lethargy or insomnia, or signs of autonomic dysfunction (ileus, acute urinary retention).

Treatment. Treatment of overdose involves general supportive treatment, including supporting respiratory and cardiac functions. Through neurological testing it is also indicated if pyridoxine poisoning is suspected, although neuropathy gradually improves following the removal of pyridoxine. Follow-up should be extended for at least seven days after acute administration of potentially toxic amounts, since delayed neurological effects have been reported.

Presentation Ampoules, (clear, colourless sterile solution for injection) 50 mg/1 mL: 5's.
Tablets, 25 mg (white, scored): 100's.
Storage Tablets. Store below 30 deg. C. Protect from light.
## 20.3 Adverse events report form

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<thead>
<tr>
<th>CTCAE Category</th>
<th>Adverse Event</th>
<th>Grade</th>
<th>Hospitalization/ Prolongation of Hospitalization</th>
<th>Comments</th>
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INFORMATION FOR PARTICIPANTS

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. If you do not wish to participate, your medical care will not be affected in any way.

You are invited to take part in this study because you will be taking capecitabine (Xeloda) chemotherapy.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out if taking daily pyridoxine (also known as vitamin B6) can prevent a potential side-effect from capecitabine chemotherapy called hand-foot syndrome (HFS). HFS is a condition affecting the hands and feet which can range from mild pins and needles, redness and swelling to skin peeling which can be painful and affect your activities.

HFS is usually managed by temporarily stopping or reducing the dose of capecitabine chemotherapy. This research is being done because HFS is a common side-effect of capecitabine, and we do not know if pyridoxine can prevent HFS. Pyridoxine is not usually given to prevent HFS from happening, but it appears to have some effect in treating HFS.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Nearly 300 people like you across Singapore will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you agree to take part in this study, you will be “randomised” to take either pyridoxine or placebo orally once daily. Randomisation means that whether you get pyridoxine or placebo will be determined by chance, like flipping a coin. Placebo is an inactive pill made to look like the pyridoxine. Placebo is used in this study as knowing whether someone is on pyridoxine or not can influence the reporting of HFS.

This is a double-blind study, that is, neither the staff (doctors and nurses) nor you will know whether you are receiving the pyridoxine or the placebo.

The pyridoxine or placebo needs to be taken every day throughout each cycle of capecitabine chemotherapy even though the capecitabine is taken for only 2 out of every 3 weeks.
If you take part in this study, you will continue to be seen by your doctor every 3 weeks just as you normally will even if you do not join the study. You will still have the same investigations and blood tests as you would even if you were not in the study. However, a trial or research nurse will contact you via phone every week to see how you are going and to make sure that you take the medications correctly.

An extra 18ml or 18cc blood sample (approximately five teaspoons) is taken at the time of your routine blood tests before your first cycle of capecitabine. It will be examined for folate and vitamin B12 levels and genetic characteristics relating to how your body breaks down capecitabine or pyridoxine. These blood tests may help us to predict who is more likely to develop side effects from capecitabine. You will not be charged for these tests.

You need to let us know if you develop any problems with HFS so that your doctor can see you about it and adjust the treatment accordingly. You also need to keep a daily record of any symptoms of HFS. A symptom diary is what we generally encourage all patients taking capecitabine to keep, regardless of whether they are in a study or not.

If the HFS is mild, you may still continue with the chemotherapy and the pyridoxine or placebo in that instance. Please contact your doctor before you use any medications (including creams) for it.

If the HFS is moderate (for example painful blisters, redness, swelling or peeling of the skin that doesn’t affect your activities) or severe (skin changes as described previously but painful enough to affect your function), you need to contact us so that your doctor can see you and adjust your treatment.

While you are in the study, you are not allowed to take any other medications or over-the-counter preparations which contain vitamin B6 or pyridoxine or moisturizing creams as this will affect the results of the study.

**HOW LONG WILL I BE IN THE STUDY?**

We think you will be in the study for a maximum of approximately 24 weeks or 8 cycles of capecitabine chemotherapy. However, if you get moderate to severe HFS as described earlier, you may be withdrawn from the study and your doctor may reduce or stop the capecitabine temporarily, with or without pyridoxine. You do not need to be in the study if you stop taking capecitabine earlier than planned for any other reason. You do not need to be followed up as part of the study after you have received 8 cycles of the chemotherapy with capecitabine. You can still continue with the chemotherapy itself if your doctor decides it is appropriate.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the research nurse and your oncologist first.

**WHAT ARE THE RISKS OF THE STUDY?**

Pyridoxine, being a type of vitamin, rarely causes any side effects. However, some adverse effects have been reported, usually at a much higher dose than what we use in this study. They include nausea, vomiting, abdominal pain, loss of appetite, headache,
tingling and drowsiness. Although a few cases of transient nervousness and tremor have been reported after stopping the pyridoxine, studies on larger series of patients have not confirmed such problems.

**WHAT ARE THE BENEFITS OF TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients taking capecitabine in the future. All patients participating in the study will get 25% discount off the usual price of capecitabine tablets for up to six cycles while on the study, eg if each cycle of capecitabine costs $800, you will receive $200 discount every cycle.

**WHAT OTHER OPTIONS ARE THERE?**

Instead of being in this study, you have these options:
- Take the capecitabine chemotherapy as instructed without pyridoxine.
- Some oncologists recommend daily pyridoxine to patients taking capecitabine even before they get HFS.
- Please talk to your regular doctor about these and other options.

**WHAT ARE THE COSTS?**

The study investigator group will provide you with pyridoxine or placebo free of charge while you are being treated on this study. Your participation in this study will not increase the amount of money you have to pay for your treatment at your institution. Apart from the 25% discount from the capecitabine chemotherapy, all other expenses, including the cost of routine standard examinations will be handled as if you were receiving standard treatment and not participating in a clinical trial.

**Compensation for Participation**

In the event that you suffer an adverse event or a medical accident during this study, treatment will be offered at the usual charge. The Hospital does not make any provisions to compensate trial subjects for research related injury. However, compensation may be considered on a case-by-case basis for unexpected injuries due to non-negligent causes.

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Your participation in this study is voluntary. You may choose not to participate and receive treatment without affecting your health care/services or other rights. You are also free to withdraw from this study at any time. Withdrawal or refusal to participate will not prejudice your health care.
In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you or your legal representative will be notified so that you can make an informed decision whether or not to continue your participation in this study.

WHAT ABOUT CONFIDENTIALITY?

Your Privacy

Your rights of privacy will be maintained in the following manner: All information obtained about you during the study will be kept as confidential as legally possible and will be accessible only to your doctors, the investigators and any appropriate government agency. By signing the informed consent form you authorise this access to your records. Should the result of this study be published, neither your name nor any information from which you may be identified will be included.

Data associated with your participation in this study will be stored on paper records and computer, and analyzed using a computer. International regulations for the handling of computerized data will be followed.

Confidentiality

Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available unless disclosure is required by law.

Data obtained from this study that does not identify you individually.

Your original medical records may be reviewed by the Singhealth Centralized Institutional Review Board (CIRB), and regulatory authorities for the purpose of verifying clinical trial procedures and/or data. By signing this consent form, you authorize the record review, information storage and data transfer described above.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions about this study or your rights, please contact Dr Yap Yoon Sim
Department of Medical Oncology
National Cancer Centre
11 Hospital Drive,
Singapore 169610
Tel: 65-64368000; Fax: 65-62272759
or
Ms …..
Clinical Trials Coordinator
Medical Oncology Clinical Trials Unit
This study has been reviewed by the Singhealth Centralized Institutional Review Board. Should you wish to discuss the project with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study or your rights as a participant, or should you wish to make a confidential complaint, you may contact the Secretary, Singhealth Centralized Institutional Review Board at (65) 6323 7515.

If you would like to take part in this research study, please sign and date the attached consent form. Your signature indicates that you have decided to take part in this research study and that you have read and understand the information given above and explained to you.

You will be given a signed copy of this form to keep.

By signing this page, I am confirming the following:

- The trial has been explained to me in a language __________________________ I understand by ______________________ on ___________.
  (STATE THE LANGUAGE USED)
  (NAME OF TRANSLATOR)         (DATE)

- I have read all the information in this Patient Information Sheet and Consent Form.

- All of my questions have been answered to my satisfaction.

- I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.

- I know that I can freely choose to stop being a part of this study at any time.

- I have received a copy of this Patient Information Sheet and Consent Form to keep for myself.

__________________________________________________________________________
Name                  Signature                  Date

__________________________________________________________________________
Name of legal representative        Signature                  Date

__________________________________________________________________________
Name of Investigator or Designee    Signature                  Date

__________________________________________________________________________
Name of Witness                          Signature                  Date

Pyridoxine Protocol
Version 6, 8 August 2011
RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF
PYRIDOXINE FOR PREVENTION OF CAPECITABINE INDUCED
HAND-FOOT SYNDROME

Biomarker Study

As part of the above research study, an extra 18ml or 18cc blood sample
(approximately five teaspoons) is taken at the time of your routine blood tests before
you commence capecitabine chemotherapy. It will be examined for folate levels and
any genetic characteristics relating to how your body breaks down capecitabine or
pyridoxine. You will not be charged for these tests. The blood samples will be coded
with no direct identification of patients from the samples, and the information will be
confidential.

If you agree to take part in this biomarker study, please sign and date the attached
consent form. Your signature indicates that you have decided to take part in this
research study and that you have read and understand the information given above
and explained to you.

You will be given a signed copy of this form to keep.

By signing this page, I am confirming the following:
• The trial has been explained to me in a language I understand by __________________ on ____________________.
• I have read all the information in this Patient Information Sheet and Consent Form.
• All of my questions have been answered to my satisfaction.
• I voluntarily agree to be part of this research study, to follow the study procedures,
  and to provide necessary information to the doctor, nurses, or other staff members,
  as requested.
• I know that I can freely choose to stop being a part of this study at any time.
• I have received a copy of this Patient Information Sheet and Consent Form to keep
  for myself.

_________________________  ________________________ ___________ _
Name         Signature        Date

_________________________  ________________________ ___________ _
Name of legal representative    Signature        Date

_________________________  ________________________     ____________
Name of Investigator or Designee                                 Signature                                      Date

_________________________  ________________________ ___________ _
Name of Witness                                 Signature                                      Date

Pyridoxine Protocol
Version 6, 8 August 2011
20.6 Capecitabine Dose Calculation according to Body Surface Area (BSA)

Dose level $\geq 1000\text{mg/m}^2$ twice daily

NB: Due to the dosage capecitabine tablets come in (500mg and 150mg tablets), for convenience, some of the doses may be rounded down slightly. The minimum dose may be slightly below $1000\text{mg/m}^2$ twice daily, but investigators may prescribe a higher dose than the minimum dose.

<table>
<thead>
<tr>
<th>Surface Area (m$^2$)</th>
<th>Minimum Total Daily Dose (mg)</th>
<th>Minimum Twice Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 1.22$</td>
<td>2300</td>
<td>1150</td>
</tr>
<tr>
<td>1.23-1.37</td>
<td>2600</td>
<td>1300</td>
</tr>
<tr>
<td>1.38-1.57</td>
<td>3000</td>
<td>1500</td>
</tr>
<tr>
<td>1.58-1.72</td>
<td>3300</td>
<td>1650</td>
</tr>
<tr>
<td>1.73-1.90</td>
<td>3600</td>
<td>1800</td>
</tr>
<tr>
<td>1.91-2.07</td>
<td>4000</td>
<td>2000</td>
</tr>
<tr>
<td>2.08-2.22</td>
<td>4300</td>
<td>2150</td>
</tr>
<tr>
<td>$\geq 2.23$</td>
<td>4600</td>
<td>2300</td>
</tr>
</tbody>
</table>
20.7 Euro-QOL (EQ-5D) QOL questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the **BLACK BOX** below to whichever point on the scale indicates how good or bad your health state is today.