# (BTD) Bendamustine, Thalidomide and Dexamethasone

## Indication
Relapsed/refractory multiple myeloma and malignant plasma cell neoplasms.

(Funding via CDF)

## ICD-10 codes
Codes with a prefix 90

## Regimen details

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 and 8 (**or** 1 and 2) | Bendamustine | 60mg/m$^2$ | IV infusion |
| 1-28 (continuously) | Thalidomide | 50mg ON for one week then 100mg ON (can escalate to a maximum of 200mg if tolerated) | PO |
| 1-4 and 15-18 | Dexamethasone | 20mg OM | PO |

## Cycle frequency
28 days

## Number of cycles
Minimum of 4 cycles, until maximum response plus 2 cycles. Up to a maximum of 9 cycles.

## Administration
Bendamustine is administered in 500mL sodium chloride 0.9% over 30-60 minutes.

Thalidomide is available as 50mg capsules. The dose should be taken at night time as thalidomide may cause sedation. It may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be advised not to drive cars, use machinery or perform hazardous tasks whilst taking thalidomide. Thalidomide may be taken with or without food.

Dexamethasone is available as 500microgram and 2mg tablets. The dose should be taken in the morning, with or after food.

Patients should be advised to remain well hydrated throughout treatment.

## Pre-medication
Nil

## Emetogenicity
This regimen has moderate emetic potential (on days 1 and 8).

## Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first week. (Omit allopurinol on days of bendamustine administration – see interactions section).
$H_2$ antagonist or PPI as per local policy
Antifungal prophylaxis as per local policy
Antiviral prophylaxis as per local policy (if previous herpetic infection)
PCP prophylaxis as per local policy (if previous autograft)
Thromboprophylaxis
Bisphosphonates as per local policy
Laxatives, if required.

## Extravasation

Bendamustine is an irritant (Group 3)

## Investigations – pre first cycle

| Investigation | Validity period |
|---|---|
| FBC and film | 72 hours |
| Clotting screen | 72 hours |
| U+E (including creatinine) | 72 hours |
| LFTs | 72 hours |
| Calcium | 72 hours |
| Glucose | 72 hours |
| Uric acid | 72 hours |
| CRP | 72 hours |
| Pregnancy test (female of child bearing potential) | 72 hours |
| Group and save (Notify transfusion laboratory for irradiated blood products) | 14 days |
| Paraprotein monitoring and/or serum free light chain assay | 7 days |
| Consider bone marrow biopsy and imaging | |

## Investigations – pre subsequent cycles

| Investigation | Validity period |
|---|---|
| FBC | 72 hours |
| U+E (including creatinine) | 72 hours |
| LFTs | 72 hours |
| Calcium | 72 hours |
| Glucose | 72 hours |
| Pregnancy test (female of child bearing potential) | Each cycle |

## Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

| Investigation | Limit |
|---|---|
| Neutrophils | ≥ 1.0 x $10^9$/L |
| Platelets | ≥ 75 x $10^9$/L |
| Pregnancy test | Negative |
| Bilirubin | < ULN |
| Creatinine Clearance | > 10 mL/min |

## Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x $10^9$/L and/or platelets < 75 x $10^9$/L withhold bendamustine until recovery.
If the cytopaenias are disease related, use G-CSF as per local policy and platelet support. Discuss with consultant.

- **Renal impairment**

There is no information regarding use of bendamustine if CrCl ≤ 10mL/min. Discuss with consultant.

- **Hepatic impairment**

| **Bilirubin** (x ULN) | **Bendamustine dose** |
|---|---|
| ≤ ULN | 100% |
| 1-3 | 70% |
| > 3 | Discuss with consultant (no information) |

- **Other toxicities**

**Neuropathy**:
Thalidomide should be stopped or reduced if there are symptoms of progressive peripheral neuropathy causing functional disability. Consider re-introducing at 50 mg/day after a two-week gap if symptoms permit. Neuropathy is often irreversible.

**Venous thromboembolism (VTE):**
Treat with full dose anticoagulation, thalidomide can continue.

## Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Thrombotic events
Neuropathy
Hypersensitivity (bendamustine)
Cardiotoxicity
Teratogenic (thalidomide)
Syncope, bradycardia and AV block

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Constipation (thalidomide)
Sedation (thalidomide)
Dizziness and orthostatic hypotension
Sleep disturbance, psychosis (steroids)

- **Other side effects**

Alopecia
Skin reactions
Fatigue
Steroid side effects

## Significant drug interactions – for full details consult product literature/ reference texts

**Warfarin/coumarin anticoagulants:** increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral vitamin K antagonist monitor the INR at least once a week and adjust dose accordingly.

**Bendamustine**

**Allopurinol:** reports of Stevens-Johnson syndrome and toxic epidermal necrolysis – avoid concurrent administration.

**CYP 1A2 inhibitors:** metabolism of bendamustine by cytochrome P450 (CYP) 1A2 isoenzyme is a significant route of hepatic clearance so interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, aciclovir and cimetidine is possible. May increase toxicity – avoid concomitant use.

**Thalidomide**

May increase **sedative** and **bradycardic** effects of other medication.

May increase **peripheral neuropathy** associated with other medication.

**Combined oral contraceptive pill**: increased risk of venous thrombo-embolic events - avoid concurrent use.

## Additional comments

Patients must receive irradiated blood products for all future transfusions.

Thalidomide is highly teratogenic.
Women of child bearing potential must have a negative pregnancy test within 3 days prior to starting treatment. Pregnancy testing should be repeated monthly thereafter until 4 weeks after stopping thalidomide (or every 2 weeks in women with irregular menstrual cycles). If a woman taking thalidomide thinks she may be pregnant she must stop the drug immediately.

Men taking thalidomide must use a barrier method of contraception throughout treatment and for one week after stopping, if their partner is capable of bearing children.

Women of child-bearing potential must use an agreed effective method of contraception for at least 4 weeks before starting thalidomide, while on thalidomide and for 4 weeks after. (The combined oral contraceptive pill is not recommended due to the increased risk of thromboembolism).

Thalidomide is supplied through the Celgene Pregnancy Prevention Programme. All patients need to be provided with the Pregnancy Prevention Programme booklet before starting treatment.
A completed Celgene Prescription Authorisation Form must be sent to pharmacy with each prescription.

## References


- Summary of Product Characteristics Bendamustine (Napp) accessed 15 July 2015 via www.medicines.org.uk
- Summary of Product Characteristics Thalidomide (Celgene) accessed 15 July 2015 via www.medicines.org.uk
- Pönisch et al., Combined bendamustine, prednisolone and thalidomide for refractory or relapsed multiple myeloma after autologous stem-cell transplantation or conventional chemotherapy: results of a Phase I clinical trial. Br J Haematol. 2008 Oct; 143(2):191-200.
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- Grey-Davies et al., British Journal of Haematology 2011:156, 545–555
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