

Systemic Anti Cancer Therapy Protocol

V-DTPACE MULTIPLE MYELOMA OR PLASMA CELL LEUKAEMIA

PROTOCOL REF: MPHAVDTHA
(Version No. 2.0)

Approved for use in:

- Myeloma where there is failure to achieve response or disease progression with induction therapy
- Relapsed or refractory myeloma suitable for intensive salvage chemotherapy
- Primary plasma cell leukaemia or initial presentation with extra medullary disease

Blueteq is not required

Dosage:

Drug	Dose	Route	Frequency
Hydration	See schedule	IV	Day 1 to 5
Cisplatin or Carboplatin	*10mg/m ² or 50mg/m ²	IV	Day 2 to 5
Etoposide	*40mg/m ²	IV	Days 2 to 5
Cyclophosphamide	*400mg/m ²	IV	Days 2 to 5
Doxorubicin	*10mg/m ²	IV	Days 2 to 5
Bortezomib	1mg/m ²	S/C	**Days 2, 5, 9 and 12
Thalidomide	100 - 400mg	PO	Days 2 to 29. Start at 100mg nocte, titrate to max 400mg nocte (typical max dose is 200mg) OMIT FROM CYCLE PRE-HSCT HARVEST
Dexamethasone	40mg***	PO	Days 2 to 5

*Consider dose capping at 2m² at clinician discretion

**Bortezomib can be administered weekly on days 1, 8, 15 and 22 of a 28 day cycle if they cannot tolerate twice weekly dosing above.

***Dexamethasone can be reduced at clinician discretion.

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Cycle length every 28 days and upon count recovery, for a maximum of 6 cycles.**

**Cycle 1 is 29 days duration due to day 1 being pre-hydration. Subsequent cycles can have hydration administered on day 28 of cycle such that chemotherapy cycles every 28 days.

Administration:

- A dual lumen Hickman line is required.
- An inpatient stay is required (at least 5 days).
- Liaise with BMT team prior to initiation.
- This regime involves a continuous infusion of fluids for 5 days and chemotherapy for 4 days.
- Patient should report any changes in hearing or balance.
- VTE prophylaxis is required throughout treatment due to thrombotic effect of thalidomide.
- Dexamethasone tablets should be taken in the morning after food.
- At least 72 hours should elapse between bortezomib administrations.
- Bortezomib should be administered subcutaneously through the thighs (right or left) or abdomen (right or left). The solution should be injected subcutaneously, at a 45-90° angle. Injection sites should be rotated for successive injections.
- Thalidomide should be taken as a single dose at bedtime, to reduce the impact of somnolence. Capsules should not be opened or crushed.
- The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the PPP and provide patients with appropriate patient educational brochure and patient card.

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Pregnancy Prevention Programme (PPP):

Due to the increased risk of birth defects associated fetal exposure to thalidomide the following should be adhered to:

- A Treatment Initiation Form (TIF) must be completed prior to treatment initiation with thalidomide
- A Prescription Authorisation Form (PAF) must be completed by the prescriber for each supply of thalidomide. This must be approved by a pharmacist when verifying each prescription and confirmation of dispensing completed by the relevant dispensing pharmacy. Supply must be completed within 7 days of the prescription generation.
- A maximum of 3 months can be supplied for men or women of non-child bearing potential
- A maximum of 1 month can be supplied for women of child bearing potential. A negative pregnancy test must be confirmed within 3 days of prescription generation.

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

Hydration associated with cisplatin:

- Hydration from day 1 (day prior to chemotherapy): 1000mL of Sodium Chloride 0.9% with 20mmol potassium chloride (0.15%) and 10mmol magnesium every 12 hours (2L per day) for 5 days.

Supportive medicines:

- Ensure supportive medications and oral chemotherapy (**including thalidomide and dexamethasone**) are transcribed as inpatient orders and available on the MAR prior to administration of chemotherapy.
- Allopurinol PO 300mg once daily for first cycle. Consider rasburicase if high risk of tumour lysis syndrome.
- Aciclovir PO 400mg twice daily is not generally required but may be given at the discretion of the prescriber.

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- Aprepitant PO 125mg once daily on day 1 and 80mg once daily on days 2 and 3
- Co-trimoxazole PO 480mg once daily (continue for 3-6 months after treatment)
- Chlorhexidine 0.2% mouthwash 10mLs four times daily
- Docusate 100mg twice a day when required
- Filgrastim 30 or 48 million units (depending on weight) subcutaneously once daily from day 7 until neutrophils are greater than $1.0 \times 10^9/L$ for 2 consecutive days. See below for information when used for mobilisation prior to haematopoietic stem cell harvesting
- Metoclopramide PO 10mg three times daily when required
- Nystatin oral suspension 1mL four times daily or fluconazole oral 50mg once daily (higher risk patients only)
- Omeprazole PO 20mg once daily
- Ondansetron IV 8mg twice daily for 5 days then oral when required
- VTE Prophylaxis:
 - Dalteparin 5,000 units subcutaneous injection daily (or alternative prophylactic low molecular weight heparin (LMWH))
 - Therapeutic dose LMWH in high risk patients. Patients may continue previously established DOAC treatment or be switched to a LMWH.
 - Aspirin oral 75mg daily (for those patients who decline LMWHs or for those deemed to be low risk on long term treatment)

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Renal and Hepatic Dosing:

Renal Dose Modifications		
NB the Wright Formula <i>must</i> be used to calculate CrCl		
Cisplatin <i>Wright Formula</i>	Creatinine Clearance (mL/min)	Dose Adjustment
	50 – 59	75% dose
	40 - 49	50% dose
	<40 or haemodialysis	Consider 50% dose or carboplatin.
Etoposide <i>Wright Formula</i>	Creatinine Clearance (mL/min)	Dose Adjustment
	10 – 50 or haemodialysis	Consider 75% dose. Increase if tolerated
Cyclophosphamide <i>Wright Formula</i>	Creatinine Clearance (mL/min)	Dose Adjustment
	10 – 29	75% dose
	<10 or haemodialysis	Not recommended. Consider 50% if unavoidable
Doxorubicin	Creatinine Clearance (mL/min)	Dose Adjustment
	Haemodialysis	Consider 75% dose
Thalidomide	No dose reduction required	
Bortezomib	No dose adjustments required but bortezomib should be administered after dialysis.	
Carboplatin	Clinician decision if creatinine clearance <20mL/min	

Hepatic Dose Modifications		
Cisplatin	No dose adjustment required	
Etoposide	Parameter	Dose Adjustment
	Bilirubin \geq 50 μ mol/L or decreased albumin levels	Consider 50%. Increase if tolerated
Cyclophosphamide	Not recommended in severe hepatic impairment due to reduced efficacy	
Doxorubicin	Bilirubin (micromol/L)	Dose Modification
	20 – 50	50% dose
	51 – 86	25% dose
	>86 or Child Pugh C	Not recommended
Thalidomide	No dose reduction required	
Bortezomib	Moderate to severe impairment	Reduce to 0.7mg/m ²
Carboplatin	No dose adjustment required	

Extravasation risk:

Cisplatin: irritant

Carboplatin: irritant

Etoposide: irritant

Cyclophosphamide: non-vesicant

Doxorubicin: vesicant

Bortezomib: non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Interactions:

Cisplatin

- Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, Amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on the kidneys and auditory function.
- Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control when phenytoin is given as current treatment. During cisplatin therapy starting new anticonvulsant treatment with phenytoin is strictly contraindicated.

Carboplatin

- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin). Avoid concomitant use.
- Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.
- Loop diuretics: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity

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Cyclophosphamide

Substances that reduce the efficacy of cyclophosphamide include:

Aprepitant, bupropion, busulfan, ciprofloxacin, chloramphenicol, azole-antimycotics (e.g., fluconazole and itraconazole, CYP2B6 and CYP3A4 inhibitors (e.g. nevirapin and ritonavir): co-administration may reduce the efficacy of cyclophosphamide, prasugrel, sulphonamides, e.g. sulfadiazine, sulfamethoxazole and sulfapyridine, thiotepa, grapefruit (fruit or juice), rifampicin, St. John's wort.

An increased risk of side-effects may occur with:

Azathioprine: increased risk of hepatotoxicity (liver necrosis), chloral hydrate, cimetidine, disulfiram, glyceraldehyde, protease inhibitors, saquinavir, rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines, corticosteroids and dabrafenib.

There is an increased risk of cardiotoxicity when co-administration with:

anthracyclines, mitomycin, cytarabine, pentostatin and radiation therapy.

Etoposide

High dose ciclosporin can result in increased accumulation of etoposide.

Concomitant phenytoin or phenobarbital therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased etoposide clearance and reduced efficacy. Co-administration of antiepileptic drugs and Etoposide injection can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

Doxorubicin

Phenytoin given with doxorubicin may reduce blood levels of the anticonvulsant and to increase seizure activity. Therapeutic drug monitoring (TDM) for phenytoin would be advised.

Concomitant administration of inhibitors of CYP450 and/or P-glycoprotein might lead to increased plasma concentrations of doxorubicin and thereby increased toxicity.

Clozapine may increase the risk/severity of the haematologic toxicity of doxorubicin

Doxorubicin may reduce oral bioavailability of digoxin.

Doxorubicin is a potent, radio sensitizing agent

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Thalidomide

Thalidomide has sedative properties, thus may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H₁antihistamines, opiate derivatives, barbiturates and alcohol. Use with caution.

Thalidomide may cause bradycardia. Use with caution alongside other medicinal products having the same pharmacodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.

Use with caution alongside other medicinal products known to be associated with peripheral neuropathy (e.g. vincristine and bortezomib).

Bortezomib

Monitor closely for side effects when giving bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) due to potential for increased exposure to bortezomib.

Concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced

For more detailed interactions please refer to the SPC.

Treatment Schedule:

Day	Time	Drug	Dosage	Route	Diluent and Rate
1	08:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
	20:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
2	08:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
	09:00	Aprepitant	125mg	PO	Mane
		Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
		Dexamethasone	40mg	PO	Mane
10:00	Cisplatin	10mg/m ²	IV		

		Etoposide	40mg/m ²		In 1000mL Sodium Chloride 0.9% over 24 hours* (all in the same bag)
		Cyclophosphamide	400mg/m ²		
		Doxorubicin	10mg/m ²	IV	In 100mL Sodium Chloride 0.9% over 24 hours*
		Bortezomib	1mg/m ²	S/C	Slow bolus
	20:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
		Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
22:00	Thalidomide	100mg – 400mg	PO	Nocte	
3	08:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
	09:00	Aprepitant	80mg	PO	Mane
		Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
		Dexamethasone	40mg	PO	Mane
	10:00	Cisplatin	10mg/m ²	IV	In 1000mL Sodium Chloride 0.9% over 24 hours* (all in the same bag)
		Etoposide	40mg/m ²		
		Cyclophosphamide	400mg/m ²		
	20:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
		Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	22:00	Thalidomide	100mg – 400mg	PO	Nocte
4	08:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
	09:00	Aprepitant	80mg	PO	Mane
		Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
		Dexamethasone	40mg	PO	Mane
	10:00	Cisplatin	10mg/m ²	IV	In 1000mL Sodium Chloride 0.9% over 24 hours* (all in the same bag)
		Etoposide	40mg/m ²		
		Cyclophosphamide	400mg/m ²		
	Doxorubicin	10mg/m ²	IV	In 100mL Sodium Chloride 0.9% over 24 hours*	

	20:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
		Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	22:00	Thalidomide	100mg – 400mg	PO	Nocte
5	08:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
		Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	09:00	Dexamethasone	40mg	PO	Mane
		Cisplatin	10mg/m ²	IV	In 1000mL Sodium Chloride 0.9% over 24 hours* (all in the same bag)
	Etoposide	40mg/m ²			
	Cyclophosphamide	400mg/m ²			
	10:00	Doxorubicin	10mg/m ²	IV	In 100mL Sodium Chloride 0.9% over 24 hours*
		Bortezomib	1mg/m ²	S/C	Slow bolus
	20:00	1000mL Sodium Chloride 0.9% + 20mmol potassium chloride (0.15%) + 10mmol magnesium		IV	Over 12 hours
		Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
22:00	Thalidomide	100mg – 400mg	PO	Nocte (continue nocte from day 2 for 28 days)	
9	10:00	Bortezomib	1mg/m ²	S/C	Slow bolus
12	10:00	Bortezomib	1mg/m ²	S/C	Slow bolus

*All infusion bags must be taken down at after 24 hours due to risk of microbial contamination. Discard any remaining chemotherapy.

If carboplatin is required in place of cisplatin then give as below (separate bags):

Day	Day	Drug	Dose	Route	Diluent and rate
2 to 5	10:00	Carboplatin	50mg/m²	IV	In 500mL glucose 5% over 24 hours
	10:00	Cyclophosphamide	400mg/m²	IV	In 250mL sodium chloride 0.9% over 24 hours
	10:00	Etoposide	40mg/m²	IV	In 250mL sodium chloride 0.9% over 24 hours
	10:00	Doxorubicin	10mg/m²	IV	In 100mL sodium chloride 0.9% over 24 hours
All other medications / hydration as initial treatment plan					

Main toxicities:

Cisplatin / Carboplatin
Nephrotoxicity - ensure adequate pre and post hydration is prescribed. Ototoxicity - assess patient for tinnitus or hearing abnormalities Bone marrow suppression
Etoposide
Bone marrow suppression, nausea, vomiting, fatigue, secondary leukemia, hypotension,
Cyclophosphamide
Bone marrow suppression, nausea, vomiting, haemorrhagic cystitis, haematuria, mucositis, abnormal hepatic function, fever
Doxorubicin
Bone marrow suppression, nausea, vomiting, diarrhoea, alopecia, colouration of the urine, cardiotoxicity, reduced appetite, conjunctivitis, mucositis
Thalidomide
Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, drowsiness, venous thromboembolism, peripheral neuropathy, injection site reactions, infusion related reactions, high blood sugars, teratogenicity
Bortezomib
Infections, herpes zoster reactivation, herpes simplex, pneumonia, thrombocytopenia, neutropenia, anaemia, leukopenia, lymphopenia, reduced appetite, hypokalaemia, hyponatraemia, dehydration, hypocalcaemia, mood disturbance, sleep disturbance, anxiety, neuropathies, peripheral sensory neuropathy, fatigue, eye swelling, conjunctivitis, vertigo, hypo/hyper-tension, nausea, vomiting, constipation, diarrhoea, abnormal hepatic enzymes, rash, pruritus, muscle pain/weakness, weight loss, hepatitis B reactivation. Rare – seizures (review if additional risk factors for seizures)

Haematopoietic Stem Cell Mobilisation:

V-DTPACE day 1 should be administered on a Monday to facilitate apheresis starting on a Monday (day 15)

Clinical Interventions Prior to Admission

- Arrange for insertion of central venous catheter if insufficient peripheral venous access – apheresis team to assess veins if clinical suspicion that inadequate. Patient may require inpatient admission (ideally ward 4 CCC) if requiring temporary central venous access (femoral vein) and not local to CCC (within 1 hour drive) or if patient is living alone.
- Ensure adequate renal, lung and cardiac function, additional investigations may be required if clinically indicated.

- Discuss with Consultant/HPCT coordinator should any of these results fall out of normal limits
- Book apheresis session in apheresis diary from Day 15.

Patient Preparation

- Complete appropriate documentation for Stem Cell Therapeutics laboratory to request cryopreservation of HPCs.
- Ensure all blood products are irradiated for a minimum of 7 days pre-harvest.
- Explain procedures of mobilisation chemotherapy and HPC-A collection to patient and discuss potential complications.
- Offer relevant written information available.
- Obtain written informed consent from patient.

Filgrastim

- Patients should be given the opportunity to be taught how to self-administer filgrastim. A district nurse referral for G-CSF administration should be completed if the patient is unsuitable for self-administration.

Day(s) of Harvesting – From Day 15

- A peripheral blood CD34 count should be checked.
 - If $<5 \times 10^6/L$ not for apheresis and discuss with the transplant team about return following day
 - if $5-10 \times 10^6/L$ not for apheresis but transplant team to consider plerixafor before returning the following morning
 - if $>10 \times 10^6/L$ for attempt at apheresis.
- One or more harvest procedures may be required to achieve minimal requirement of 2.5×10^6 CD34⁺/kg, usually target $4-8 \times 10^6$ CD34⁺/kg. If results are not within target range clarify with consultant in charge.

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Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2+	Ongoing
Clinical Assessment	x	x	x	Every cycle
SACT Assessment (including PS and toxicity assessment)		x	x	Every cycle
FBC, U&E & LFTs & Magnesium, CrCl (Wright)	x	x	x	Every cycle
Celgene pregnancy prevention program consent	x			
Celgene prescription authorization form		x	x	Every cycle
Pregnancy Test if woman of child bearing potential		x	x	Every cycle
Bone profile	x	x	x	Every cycle
Screen for Hep B/C and HIV	x			
Dental Assessment	x			
HbA1C and blood glucose	x			Repeat as clinically indicated
Serum ig/ electrophoresis/ serum light chains (if indicated)	x	x	x	Every cycle
Imaging as per NICE/ network guidance	x			Repeat as clinically indicated
CT scan**	x			At the end of treatment and if clinically indicated
Informed Consent	x			
Echo and ECG	x			ECG /ECHO for all patients should be documented before starting anthracycline, unless stated by the medical team that this is not required
Weight recorded	x	x	x	Every cycle
Height	x			

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Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC $\geq 1.0 \times 10^9/L$	Platelets $\geq 100 \times 10^9/L$
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If cytopenias are thought to be caused by disease then treatment delay may not be indicated – clinical decision.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

See section 'Renal and Hepatic Dosing'.

Peripheral Neuropathy:

Bortezomib	
If there are symptoms of peripheral neuropathy the dose reduction schedule below must be invoked. Bortezomib should be stopped if symptoms or signs progress despite this	
Grade 1 with pain or grade 2	Reduce to 1.0mg/m ² or reduce to 1.3mg/m ² weekly (day 1 and 8)
Grade 2 with pain of grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7mg/m ² weekly (day 1 and 8)
Grade 4 and/or severe autonomic neuropathy	Discontinue
Cisplatin / Carboplatin	
Grade 2 or above should be discussed with consultant, as dose reduction of cisplatin / carboplatin may be required.	
Thalidomide	
Thalidomide should be stopped if there are symptoms of peripheral neuropathy causing pain or functional disability (grade 2 or above). If symptoms resolve to grade 1 or better (or back to normal baseline) cautious reintroduction at a dose of 50mg should be considered, escalating in 50mg increments as symptoms permit.	

Ototoxicity

Grade 2 or above should be discussed with consultant as dose reduction of cisplatin / carboplatin may be required.

References:

1. Summary of Product Characteristics for Cisplatin (Hospira), Updated June 2021, viewed July 2023 (available at <https://www.medicines.org.uk/emc>)
2. Summary of Product Characteristics for Carboplatin (Hospira), Updated June 2023, viewed July 2023 (available at <https://www.medicines.org.uk/emc>)
3. Summary of Product Characteristics for Etoposide (Medac), updated November 2022, viewed July 2023 (available at <https://www.medicines.org.uk/emc>)
4. Summary of Product Characteristics for Cyclophosphamide (Sandoz), updated April 2021, viewed July 2023 (available at <https://www.medicines.org.uk/emc>)
5. Summary of Product Characteristics for Doxorubicin (Pfizer), updated April 2021, viewed July 2023 (available at <https://www.medicines.org.uk/emc>)
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8. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019;20: e201–08.
9. VDTSPACE/DTPACE. Thames Valley Strategic Clinical Network. Version 2.1 June 2023. <https://nssg.oxford-haematology.org/myeloma/pdf-protocols/MM-50-vtdpace-dtpace.pdf>

Circulation/Dissemination

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Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
March 2020	V1.0	Hannah Greaves – Medicines Safety Officer	New protocol
Oct 2023	V2.0	Jennifer Gibson – Principal Pharmacist HO	Transferred to new template. Treatment schedule updated. Carboplatin information added. PPP section added. Administration comments updated. HSCT section added. ECG/ECHO investigations information standardised

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