riTUXimab, Methotrexate, Procarbazine and vinCRIStine (R-MPV) – 14 Days Induction Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of newly diagnosed primary CNS lymphoma (PCNSL)	C85	00664a	N/A

* This applies to post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment is administered once every 14 days for 5 to 7 cycles.

- Patients who fail to achieve a complete response (CR) after 5 cycles can be considered for two additional cycles of R-MPV.
- Patients should be considered for radiotherapy or stem cell transplantation after chemotherapy.
- After chemo-radiotherapy or chemotherapy, patients should be considered for two cycles of consolidation high-dose cytarabine.
- Patients with malignant cytology from cerebrospinal fluid (CSF) or high risk of leptomeningeal disease should be considered for intrathecal methotrexate between cycles of high dose IV methotrexate.

Please Refer to NCCP Regimen 00666 High Dose Cytarabine Consolidation Therapy (post R-MPV) which is used after riTUXimab, Methotrexate, Procarbazine and vinCRIStine (R-MPV) – 14 Days Induction Therapy

Note:

- **Hydration, alkalinisation and folinic acid therapy required with high dose methotrexate (See Table below)**

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1 to 7	Procarbazine[1]	100mg/m^2 ONCE a day	PO	N/A	**Cycles 1, 3, 5 and 7 only**
2	1	riTUXimab[2]	500mg/m^2	IV infusion[3] Observe post infusion	500mL NaCl 0.9% at a maximum rate of 400mg/hour[3]	Every 14 days
3	2	vinCRIStine[4]	1.4mg/m^2 (max 2mg)	IV infusion	50mL NaCl 0.9% over 10 minutes	Every 14 days
4	2	Methotrexate[5]	3,500mg/m^2	IV infusion	500mL NaCl 0.9% over 2 hours	Every 14 days
5	3	Folinic Acid (Calcium leucovorin)	15mg/m^2 every 6 hours	IV infusion	100mL NaCl 0.9% over 10 minutes. Commence 24 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is below the lower limit of normal on the assay threshold (See Table 2 or Table 3 below for calculation of dose of folinic acid based on methotrexate levels)[6]	Every 14 days

[1] Procarbazine is available as 50mg capsules, round dose to nearest 50mg.

[2] Consideration can be given to the administration of riTUXimab on Day 2 if more suitable for certain patients.

[3] See Table 1: Guidance for administration of riTUXimab.

[4] vinCRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer: Available on the NCCP website

[5] **Methotrexate:** See below for suggested hydration, alkalinisation regimen to be followed with methotrexate **or** Refer to local policy.
GFR to be calculated prior to administration of methotrexate infusion**.**
Adequate hydration and urine output are essential for the rapid clearance of methotrexate.

- Commence pre-hydration with sodium bicarbonate containing infusions at 125mL/m^2/hr at least 6 hours prior to methotrexate infusion.
  - Alkalinisation can be achieved with 50mmol of sodium bicarbonate over 8 hours in 1000mL NaCl 0.9%.
- **Hydration** with at least 3L/m^2/24 hours of **IV fluids** throughout treatment is essential until the methotrexate level is below the lower limit of normal on the assay.
- Urine pH should be ≥ 7.0 prior to commencement and during the methotrexate and folinic acid rescue. Check urine pH at regular intervals (6 hourly).

(This volume administered for alkalinisation is included in the total volume of hydration.)

- Check urine pH at regular intervals (6 hourly).
- If the target pH is not reached adjust the sodium bicarbonate concentration to maintain the urinary pH ≥ 7.0.
- **Potassium** should be supplemented according to the local policy.
- Check **fluid balance** at regular intervals (4 hourly) through each day (furosemide may be administered if fluid output falls below 400mL/m^2 in a 4 hour period or weight gain of >1kg from baseline or positive fluid balance of >1L).
- **Methotrexate levels** must be taken, beginning 48 hours after the start of the methotrexate infusion, every 24 hours as appropriate after commencement of the initial methotrexate infusion (book levels in advance with lab) until clearance of methotrexate.

Continue alkalinisation, hydration and folinic acid rescue (Table 2 or 3) until methotrexate level is below the lower limit of normal on the assay threshold.

[6] See Table 3 for an alternative folinic acid rescue table (using a methotrexate cut-off level of 0.04 micromol/L), as agreed by clinical reviewer, for calculation of folinic acid rescue.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Table 1: Guidance for administration of riTUXimab

The recommended initial rate for infusion is 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions can be infused at an initial rate of 100 mg/hour, and increased by 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour. Development of an allergic reaction may require a slower infusion rate. See Hypersensitivity/Infusion reactions under Adverse Effects/Regimen Specific Complications below. Any deviation from the advised infusion rate should be noted in local policies.
Recommended observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.
Rituximab should be diluted to a final concentration of 1-4mg/mL.
Rapid rate infusion schedule[ii] See NCCP guidance Available on the NCCP website . If patients did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of rituximab administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions. Initiate at a rate of 20% of the total dose for the first 30 minutes and then 80% of the dose for the next 60 minutes (total infusion time of 90 minutes). If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions. Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

Table 2: Folinic acid rescue table based on methotrexate target level <0.1micromol/L

Time after starting Methotrexate infusion	Methotrexate Plasma Concentration micromol/L				
	<0.1	**0.1-2**	**2-20**	**20-100**	**>100**
48 hours	No folinic Acid	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours
72 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
96 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
120 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
If serum creatinine increases by more than 50% above baseline at 24 hours increase folinic acid rescue.					
At time points over 120 hours continue folinic acid as recommended for 120 hours.					
Folinic acid rescue should continue for at least 72 hours.					
Once the folinic acid dose has been escalated, the dose should not be de-escalated according to response.					

Note:

- **Different tables and methotrexate target levels may be employed locally due to different practice and methotrexate serum monitoring.**
- **See alternative table below (with alternative methotrexate cut-off level of 0.04 micromol/L) (Table 3) which may be employed locally. Table 3 is based on expert guidance and has been agreed by clinical reviewer.**
- **To note: Table 2 OR Table 3 may be employed depending on local practice.**

Table 3: Alternative folinic acid rescue table based on methotrexate target level <0.04micromol/L (Provided by Beaumont RCSI Cancer Centre)

Methotrexate Plasma Conc. (µmol/L)	Folinic Acid Dose at 48 hrs (QDS for minimum of 48 hrs. Continue until methotrexate plasma conc <0.04 µmol/L)	Folinic Acid Dose at 72 hrs and subsequently (QDS for minimum of 48 hrs. Continue until methotrexate plasma conc <0.04 µmol/L)
<0.04	30mg – continue folinic acid to give 12 doses in total	30mg – continue folinic acid to give 12 doses in total
0.04 to ≤ 0.1	30mg – continue folinic acid to give 12 doses in total	50 mg/m^2
0.1 to ≤ 0.5	50 mg/m^2	100 mg/m^2
0.5 to ≤ 1.0	100 mg/m^2	200 mg/m^2
1.0 to ≤ 2.0	200 mg/m^2	At least 200 mg/m^2 (at consultant discretion)
>2.0	At least 200 mg/m^2 (at consultant discretion)	At least 200 mg/m^2 (at consultant discretion)
This table is a guide and doses of folinic acid may be changed based on individual patient characteristics. Doses should not be de-escalated once methotrexate levels begin to drop.		
Doses greater than 30mg should be given intravenously.		
Consideration may be given to the use of glucarpidase for use in patients who are experiencing methotrexate-induced renal dysfunction, high methotrexate levels (>2.0) or delayed methotrexate elimination. **Refer to local policy.**		

ELIGIBILITY:

- Indications as above
- Adequate renal function prior to receiving full dose of methotrexate. Refer to dose modifications section.

CAUTION:

- Use with caution in patients with pre-existing immunodeficiency
- The incidence of neurotoxicity related to the combination of radiotherapy and high dose methotrexate is significantly higher in patients aged older than 60 years.

EXCLUSIONS:

- Hypersensitivity to riTUXimab, methotrexate, vinCRIStine, procarbazine or any of the excipients

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist or Consultant Haematologist working in the area of haematological malignancies. Treatment should be given in a specialist inpatient unit with appropriate expertise in high dose methotrexate.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- ECG and/or ECHO
- Ophthalmologic examination to assess for ocular involvement
- Lumbar puncture with CSF for immunophenotyping
- CSF cytology
- CSF flow-cytometry
- Bone marrow aspirate and biopsy
- Pregnancy test as applicable
- Virology screen* - Hepatitis B (HBsAg, HBcoreAb) & Hepatitis C, HIV

*(Reference Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

- FBC, renal and liver profile prior to each cycle
- LDH

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose reductions of methotrexate should be considered in patients who have persistently high methotrexate levels, renal impairment or severe toxicity from methotrexate in the prior cycle.

Haematological:

Table 4: Dose modification in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1.0	and	≥100	100%
<1.0	And/or	<100	Clinical decision

Renal and Hepatic Impairment:

Table 5: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
riTUXimab[a]	Renal impairment: no need for dose adjustment is expected Haemodialysis: no dose adjustment is needed		Hepatic impairment: no need for dose adjustment is expected
Methotrexate[b]	**CrCl (mL/min)**	**Dose**	Hepatic impairment: no need for dose adjustment is expected Bilirubin > 86 µmol/L: avoid use
	≥50	No dose adjustment is needed	
	20-50	50% of the original dose	
	<20	Not recommended. If unavoidable consider haemodialysis.	
	Haemodialysis	Not recommended. If unavoidable, 50% of the original dose, can be dialysed with daily high flux dialysis.	
vinCRIStine[c]	Renal impairment: no need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		Bilirubin > 51 µmol/l: 50% of original dose
Procarbazine[d]	**CrCl (mL/min)**	**Dose**	Hepatic impairment: no need for dose adjustments is expected
	≥10	No dose adjustment is needed	
	<10	Not recommended	
	Haemodialysis	Not recommended	

[a] riTUXImab: Renal and hepatic – Giraud et al 2023
[b] Methotrexate: Renal and hepatic – Giraud et al 2023
[c] vinCRIStine: Renal and hepatic – Giraud et al 2023
[d] Procarbazine: Renal and hepatic – Giraud et al 2023

Management of adverse events:

Table 6: Dose Modification schedule of riTUXimab based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Severe infusion related reaction (e.g. dyspnoea, bronchospasm, hypotension or hypoxia) First occurrence		Interrupt infusion immediately. Evaluate for cytokine release/tumour lysis syndrome (appropriate laboratory tests) and pulmonary infiltration (chest x -ray). Infusion may be restarted on resolution of all symptoms, normalisation of laboratory values and chest x-ray findings at no more than one-half the previous rate.
Second occurrence	Consider discontinuing treatment	Consider coverage with steroids for those who are not already receiving steroids.
Mild or moderate infusion-related reaction		Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms.

Table 7: Dose modification of vinCRIStine based on neurotoxicity* (CTCAE v4.0)

Symptom	Dose of vinCRIStine
Grade 1	100%
Grade 2	Hold until recovery then reduce dose by 50%
Grade 3, 4	Omit

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting – Available on the NCCP website

riTUXimab: Minimal **(Refer to local policy)**
Methotrexate: Moderate **(Refer to local policy)**
vinCRIStine: Minimal **(Refer to local policy)**
Procarbazine: Moderate to High **(Refer to local policy)**

Note:

- Consideration should be given to classifying this regimen as moderately emetogenic.
- Patients may be at increased risk of PJP due to receipt of high dose steroids prior to initiation of R-MPV; dexAMETHasone should be discontinued or omitted post methotrexate.
- It is recommended that oral aprepitant (+ 5-HT3 receptor antagonist) is used post treatment in place of dexAMETHasone.

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) – Available on NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) – Available on NCCP website

PREMEDICATIONS:

Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of riTUXimab. Consider the inclusion of a glucocorticoid in patients not receiving glucocorticoid-containing chemotherapy.

Table 8: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO
Chlorphenamine	10mg	IV bolus
Hydrocortisone	100mg	IV bolus (60 minutes before riTUXimab)

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy).**
- PJP prophylaxis **(Refer to local policy). Consider interactions between methotrexate and co-trimoxazole.**
    - Due to treatment intensity, an alternative PJP prophylaxis to co-trimoxazole should be considered at the discretion of the primary consultant.
    - **If co-trimoxazole cannot be avoided, cease PJP prophylaxis at least 48 hours prior to methotrexate infusion and recommence upon neutrophil recovery and clearance of methotrexate.**
- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy).**
- G-CSF prophylaxis for 3 to 5 days after each cycle **(Refer to local policy).**

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **Hepatitis B Reactivation**: Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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2. Omuro, A.M.P. et al. Randomized phase II study of rituximab, methotrexate (MTX), procarbazine, vincristine, and cytarabine (R-MPV-A) with and without low-dose whole-brain radiotherapy (LD-WBRT) for newly diagnosed primary CNS lymphoma (PCNSL). Journal of Clinical Oncology 2020 38:15_suppl, 2501-2501. DOI: 10.1200/JCO.2020.38.15_suppl.2501 Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 2501-2501.
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4. Howard SC et al. Preventing and Managing Toxicities of High-Dose Methotrexate. Oncologist. 2016 Dec; 21(12):1471-1482. doi: 10.1634/theoncologist.2015-0164. Epub 2016 Aug 5. PMID: 27496039; PMCID: PMC5153332.
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8. Methotrexate Summary of Product Characteristics.Last updated: 27/10/2023. Accessed July 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-061-002_27102023161846.pdf
9. vinCRIStine sulphate 1mg/mL. Summary of Product Characteristics. Last updated: 09/10/2023. Accessed July 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-232-001_06122024145750.pdf
10. Procarbazine 50mg capsules. Summary of Product Characteristics. Last updated: 10/12/2014. Accessed July 2024. Available at: https://www.medicines.org.uk/emc/product/3732/smpc/print

Version	Date	Amendment	Approved By
1	01/12/2022		Prof Patrick G Morris, Dr Liam Smyth
2	15/11/2024	Regimen reviewed. Treatment section updated (text and table, including	Prof Patrick G Morris, Dr Liam Smyth

		footnotes). Table 2 amended. Addition of Table 3 (alternative table). Eligibility amended. Baseline tests amended. Renal and Hepatic dose modifications updated to align with Giraud et al (2023). Emetogenic potential amended as per NCCP standard wording. Adverse effects and drug interactions removed and regimen specific complications amended as per NCCP standard wording.	

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

[ii] The rapid infusion is an unlicensed means of administration of riTUXimab for the indications described above, in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.