vinCRIStine, Irinotecan and Temozolomide (VIT) Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
For the treatment of relapsed/refractory rhabdomyosarcoma in adults.	C49	00757a	N/A

*This is for post 2012 indications only

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

vinCRIStine is administered on Day 1 and Day 8, temozolomide and irinotecan are administered on Days 1 to Day 5 of a 21 day cycle.

The starting dose of temozolomide is 125 mg/m^2 once daily from Day 1 to Day 5, increasing to 150 mg/m^2 once daily from Cycle 2 (for patients without grade ≥ 3 toxicity).

Treatment is continued for up to 12 cycles or until disease progression or unacceptable toxicity develops.

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, 8	vinCRIStine [a]	1.5mg/m^2 (max 2mg)	IV infusion	50mL minibag 0.9% NaCl over 15 minutes	Every 21 days for up to 12 cycles
2	1-5	Temozolomide [b, c, d]	125mg/m^2	PO		Cycle 1
2	1-5	Temozolomide [b, c, d, e]	150mg/m^2	PO		Cycle 2 onwards every 21 days for up to 12 cycles
3	1-5	Irinotecan	50mg/m^2	IV infusion	100mL NaCl 0.9% over 60 minutes	Every 21 days for up to 12 cycles

[a] 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 Here.

[b] Temozolomide hard capsules should be administered in the fasting state.
The capsules must be swallowed whole with a glass of water and must not be opened or chewed.
If vomiting occurs after the dose is administered, a second dose should not be administered that day.

[c] Temozolomide should be administered at least one hour prior to irinotecan.

[d] If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours.

[e] The dose of temozolomide may be increased to 150mg/m^2 from cycle 2 if no toxicity effects of grade >3 are experienced.

ELIGIBILITY:

- Indications as above
- Age > 6 months and ≤ 50 years
- Patients ≤ 12 years of age Lansky Play Score 70-100%
- Patients > 12 years of age ECOG 0-2
- Adequate haematological, renal and liver status

CAUTION:

- In patients known to be homozygous for UGT1A1*28 consideration may be given to a reduced irinotecan starting dose

EXCLUSIONS:

- Hypersensitivity to vinCRIStine, temozolomide, irinotecan or to any of the excipients
- Chronic inflammatory bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Bilirubin > 3 x ULN
- Severe bone marrow failure
- Impaired renal function

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- Virology screen - Hepatitis B (HBsAg, HBcoreAb)
  *(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

- FBC, renal and liver profile prior to each cycle

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

Table 1: Dose reduction levels for irinotecan, vinCRIStine and temozolomide

	Irinotecan	vinCRIStine	Temozolomide	Temozolomide
Starting Dose	**50mg/m²**	**1.5mg/m²**	**125mg/m²**	**150mg/m²**
Level -1	40 mg/m² (80%)	0.75mg/m² (max 1mg)	100 mg/m² (80%)	120 mg/m² (80%)
Level -2	30 mg/m² (60%)	n/a	75 mg/m² (60%)	90 mg/m² (60%)
Level -3	Discontinue	n/a	Discontinue	Discontinue

Haematological:

Table 2: Dose modification in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose modification 1st occurrence	Dose modification 2nd occurrence
≥ 1.0	or	≥ 100	100% dose	100% dose
< 1.0 but recovered on day 21 after the start of a cycle	or	< 100 but recovered on day 21 after the start of a cycle	100% dose	100% dose
< 1.0 but recovered between 22 to 28 after the start of a cycle	or	< 100 but recovered between 22 to 28 after the start of a cycle	Decrease temozolomide to dose level -1	Decrease temozolomide to dose level -2 Decrease irinotecan to dose level –1
< 1.0 but recovered between 29 to 34 after the start of a cycle	or	< 100 but recovered between 29 to 34 after the start of a cycle	Decrease temozolomide to dose level -1 Decrease irinotecan to dose level-1	Decrease temozolomide to dose level –2 Decrease irinotecan to dose level -2
< 1.0 on day 34 after the start of a cycle	or	< 100 on day 34 after the start of a cycle	Discontinue study treatment	n/a

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
vinCRIStine[a]	No dose adjustment is needed		Bilirubin > 51 µmol/L	50% of original dose
	Haemodialysis: no need for dose adjustment is expected			
Irinotecan[b]	**CrCl (mL/min)**	**Dose**	Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN.	
	≥ 10	No need for dose adjustment is expected		
	< 10	Start with 50-66% of the original dose, increase if tolerated.		
	Haemodialysis	Start with 50-66% of the original dose, increase if tolerated.		

Temozolomide[c]	CrCl (mL/min)	Dose		Dose
	≥ 36	No dose adjustment is needed	Child-Pugh A/B	No dose adjustment is needed
	< 36	No need for dose adjustment is expected	Child-Pugh C	No need for dose adjustment is expected
	Haemodialysis	No need for dose adjustment is expected		

[a] vinCRIStine (renal and hepatic - Giraud et al 2023)
[b] Irinotecan (renal - Giraud et al 2023; hepatic as per SPC)
[c] Temozolamide (renal and hepatic - Giraud et al 2023)

Management of adverse events:

Table 4: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Diarrhoea:	
• Grade ≥ 3 for ≥ 3 days despite symptomatic treatment	Reduce **irinotecan** dose by 1 dose level to Level-1 for next cycle If diarrhoea ongoing on day 21, delay next cycle for up to 2 weeks until diarrhoea resolves to < Grade 1. If Grade ≥ 3 diarrhoea persists > 2 weeks despite suitable symptomatic treatment, discontinue.
• Grade ≥ 3 at reduced dose level (Dose level -1)	Reduce **irinotecan** dose further by 1 dose level to Level-2 for next cycle. If diarrhoea ongoing on day 21, delay next cycle for up to 2 weeks until diarrhoea resolves to < Grade 1. If Grade ≥ 3 diarrhoea persists > 2 weeks despite suitable symptomatic treatment, discontinue.
Other non-haematological toxicities: • Grade 3	Decrease both irinotecan and temozolomide to level -1
• Grade 3 at reduced dose level (Dose level -1)	Discontinue
• Grade 4	Discontinue

Table 5: 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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

vinCRIStine: Minimal **(Refer to local policy)**
Temozolomide: Moderate to high **(Refer to local policy)**
Irinotecan: Moderate **(Refer to local policy)**

PREMEDICATIONS:

Prophylactic atropine sulphate – see adverse effects below.
Atropine should not be used in patients with glaucoma **(See Adverse Effects/Regimen specific complications below).**

OTHER SUPPORTIVE CARE:

- Prophylactic regimen against vinCRIStine-induced constipation is recommended **(Refer to local policy)**
- Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle
  - As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal therapy must be initiated immediately
  - The currently recommended anti-diarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours)
  - This therapy should continue for 12 hours after the last liquid stool and should not be modified
  - In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours
  - Noting that cefixime was used in the supporting trial, this agent maybe considered in adults at a dose of 400 mg orally once daily from day-2 to day +7
- Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur
- PJP prophylaxis required with temozolomide **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.

vinCRIStine:

- **Neuropathy:** vinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months.
- **Constipation:** A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.
- **Extravasation:** vinCRIStine causes pain and possible tissue necrosis if extravasated **(Refer to local policy).**

Irinotecan:

- **Acute cholinergic syndrome**: If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation) atropine sulphate (0.25mg subcutaneously) should be administered unless clinically contraindicated. Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan. The dose of atropine sulphate may be repeated if required.
- **Diarrhoea:** Irinotecan induced diarrhoea can be life threatening and requires immediate management (See supportive care above also)
    - Diarrhoea (early onset) - see acute cholinergic syndrome above
    - Diarrhoea (late onset):
        - Irinotecan induced diarrhoea can be life threatening and requires immediate management.
        - In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan
        - Patients with an increased risk of diarrhoea are those who had previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women
        - In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles
        - A prophylactic broad-spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 0.5 x 10^9/L)

- **Gilbert's Syndrome:** Increases the risk of irinotecan-induced toxicity. A reduced initial dose should be considered for these patients.
- **Respiratory disorders:** Severe pulmonary toxicity has been reported rarely. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan therapy.
- **Cardiac disorders:** Myocardial ischaemic events have been observed predominantly in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy.
- **Other:** Since this medicinal product contains sorbitol, it is unsuitable in hereditary fructose intolerance.

Temozolomide:

- **Opportunistic infections and reactivation of infections**: Opportunistic infections (such as Pneumocystis jirovecii pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with temozolomide.
- **Pneumocystis jirovecii pneumonia (PJP):** There may be a higher occurrence of PJP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving steroids, should be observed closely for the development of PJP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using temozolomide, in particular in combination with dexamethasone or other steroids.
- **Hepatitis B Virus (HBV):** Hepatitis due to HBV reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.
- **Hepatotoxicity:** Hepatic injury, including fatal hepatic failure, has been reported in patients treated with temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide.

DRUG INTERACTIONS:

- CYP enzyme inducers may increase the clearance of irinotecan and vinCRIStine thus decreasing efficacy.
- CYP enzyme inhibitors may decrease the clearance of irinotecan and vinCRIStine.
- Concurrent administration of vinCRIStine with allopurinol, pyridoxine or isoniazid may increase the incidence of cytotoxic induced bone marrow depression.
- No studies have been conducted to determine the effect of temozolomide on the metabolism or elimination of other medicinal products.
- Since temozolomide does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products.

- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
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5. Irinotecan (CAMPTO®) Summary of Product Characteristics. Last updated: 09/05/2022. Accessed 02/06/2022. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-212-001_10062024115833.pdf
6. Temozolomide (Temodal®) Summary of Product Characteristics. Last updated: 14/07/2021. Accessed 02/06/2022. Available at: https://www.ema.europa.eu/en/documents/product-information/temodal-epar-product-information_en.pdf

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1	11/06/2024		Dr Mark Doherty

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.