Trabectedin Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents	C49	00374a	Hospital

**If the reimbursement status is not defined [1], the indication has yet to be assessed through the formal HSE reimbursement process.*

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.

Trabectedin is administered as an intravenous infusion over 24hours once every 21 days until disease progression or unacceptable toxicity occurs.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Trabectedin	1.5mg/m^2	IV infusion	1000 ml 0.9% NaCl over 24 hours	Every 21 days
*Concentration of trabectedin in the infusion solution being ≤ 0.030 mg/ml. Intravenous administration through a central venous line is strongly recommended					

Table 1: Pre-treatment haematological, renal and liver criteria required before treatment with trabectedin

ANC	≥ 1.5 x10^9/L	Patients should not proceed with treatment with trabectedin unless these pre-treatment criteria are met. If pre-treatment criteria are not met, treatment should be held. Treatment may be held for up to 3 weeks. If criteria are still not met after delay consider discontinuation of treatment or dose reduction (Reference Dose Modifications below)
Platelets	≥ 100 x10^9/L	
Haemoglobin	≥ 9 g/dl	
Albumin	≥ 25 g/L	
Bilirubin	≤ULN	
Alkaline phosphatase	≤2.5 x ULN	
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	≤2.5 x ULN	
Creatinine clearance (CrCl)	≥30 ml/min	
Creatine phosphokinase (CPK)	≤2.5 x ULN	

*ULN = Upper limit of normal

ELIGIBILTY:

- Indications as above
- ECOG performance status 0-1
- Adequate haematological, renal and hepatic function (see Table 1 above)

EXCLUSIONS:

- Hypersensitivity to trabectedin or any of the excipients

- Concurrent serious or uncontrolled infection
- Breast-feeding
- Pregnancy

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, liver and renal profiles, CPK
- MUGA or ECHO (to determine LVEF)

Regular tests:

- FBC, renal and liver profiles, CPK weekly during first two cycles of therapy and at least once between treatments in subsequent cycles.

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.
- The same dose should be given for all cycles provided that no grade 3-4 toxicities are seen and that the patient meets the re-treatment criteria as shown in Table 1.
- If any of the events listed in table 2 occur at any time between cycles, the dose must be reduced one level, according to table 3 below, for subsequent cycles

Table 2: Dose modification of trabectedin based on adverse events

Adverse event	Dose Modification
ANC < 0.5 x 10^9/L for > 5 days or associated with fever or infection	Reduce dose by one level according to table 3 below, for subsequent cycles. Once dose has been reduced dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in patient exhibiting clinical benefit, the dose may be further reduced (see Table 3). Colony stimulating factors can be administered for haematologic toxicity **(Refer to local policy)**
Platelets < 25 x 10^9/L	
Increase of bilirubin > ULN and/or alkaline phosphatase > 2.5 x ULN	
Increase of aminotransferases (AST or ALT) > 2.5 x ULN	
Any other grade 3 or 4 adverse reactions	

Table 3: Dose modification table for trabectedin for soft tissue sarcoma

Starting dose	1.5mg/m^2
First reduction	1.2 mg/m^2
Second reduction	1 mg/m^2

Renal and Hepatic Impairment:

Table 4: Dose modification of trabectedin in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
Considering the pharmacokinetic characteristics of trabectedin, no dose adjustments are warranted in patients with mild or moderate renal impairment.	Special caution is advised and dose adjustments may be necessary in patientswith hepatic impairment since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin must not be treated with trabectedin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS:

All patients must receive corticosteroids e.g. 20 mg of dexamethasone intravenously 30 minutes prior to trabectedin not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects.

OTHER SUPPORTIVE CARE:

No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Cardiac Dysfunction:** It is recommended to monitor patients for clinical cardiac signs or symptoms. It is also recommended to monitor LVEF at baseline and periodically during the treatment; particularly in patients at risk of cardiomyopathy from previous anthracycline exposure or in patients with symptoms of decreasing cardiac function.
- **Rhabdomyolosis and severe CPK elevations (> 5 x ULN**): Trabectedin must not be used in patients with CPK > 2.5 x ULN. Rhabdomyolysis has been uncommonly reported, usually in association with myelotoxicity, severe liver function test abnormalities and/or renal or multiorgan failure. Therefore, CPK should be closely monitored whenever a patient may be experiencing any of these toxicities or muscle weakness or muscle pain. If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Treatment with trabectedin should be discontinued until the patient fully recovers. Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. statins), are administered concomitantly with trabectedin, since the risk of rhabdomyolysis may be increased
- **Injection site reactions:** The use of central venous access is strongly recommended Patients may develop a potentially severe injection site reaction when trabectedin is administered through a peripheral venous line. Trabectedin extravasation may cause tissue necrosis requiring debridement.
- **Allergic Reactions:** During postmarketing experience, hypersensitivity reactions with very rare occurrence of fatal outcome, have been reported in association with trabectedin administration either alone or in combination with pegylated DOXOrubicin.

DRUG INTERACTIONS:

- Trabectedin is metabolized mainly by CYP3A4. Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors and such combinations should be avoided if possible. If such combinations are needed, appropriate dose adjustments should be applied in the event of toxicities.
- Concomitant use of trabectedin with strong CYP3A4 inducers should be avoided if possible
- Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product
- Preclinical data have demonstrated that trabectedin is a substrate to P-gp. Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. central nervous system (CNS) toxicity has not been established. Caution should be taken in such situations.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Trabectedin L01CX01

REFERENCES:

1. Demetri GD, von Mehren M, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. Clin Oncol. 2016;34(8):786.
2. Le Cesne A, Blay JY, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol. 2005;23(3):576
3. Yondelis Summary of Product Characteristics. Accessed Oct 2018. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Product_Information/human/000773/WC500045832.pdf

Version	Date	Amendment	Approved By
1	11/11/2016		Prof Maccon Keane
2	26/11/2018	Updated with NCCP regimen template. Standardisation of administration fluid and dosing in hepatic impairment	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/