Trastuzumab Emtansine (Kadcyla®) - 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for locally advanced or metastatic disease, or Developed disease recurrence during or within six months of completing adjuvant therapy.	C50	00206a	ODMS

If areimbursement indicator (e.g. ODMS, CDS[1]) is not defined, the drug and its detailed indication have not gone through the formal reimbursement process as legislated for in the Health (Pricing and Supply of Medical Goods) Act 2013.

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 on Day 1 of a 21 day cycle until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when trastuzumab emtansine is administered.

Drug	Dose	Route	Diluent & Rate	
Trastuzumab emtansine	3.6mg/kg	IV	250ml 0.9% NaCL over 90 minutes*.	
*Observe for 1 hour 30 min post-infusion. The infusion site should be closely monitored for possible subcutaneous infiltration during administration If no infusion reaction observed in Cycle 1, may give subsequent doses over 30 minutes. Observe during the infusion and for 30 minutes post- infusion.				
Use of 0.22 micron in-line polyethersulfone (PES) filter is required				

ELIGIBILTY:

- Indications as above
- HER-2 positive tumour as demonstrated by a validated test method
- ECOG 0-2 LVEF ≥ 50%

EXCLUSIONS:

- Hypersensitivity to trastuzumab or any of the excipients.
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months).

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- Blood, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)

Regular tests:

- Blood, renal and liver profile prior to each cycle
- Cardiac function every 12 weeks. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate.

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
- Management of symptomatic adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of trastuzumab emtansine as per guidelines provided in text and Tables 1 to 5.
- The dose of trastuzumab emtansine should **not** be re-escalated after a dose reduction is made.
- If a planned dose is missed, it should be administered as soon as possible; do not wait until the next planned cycle.

The schedule of administration should be adjusted to maintain a 3-week interval between doses. The next dose should be administered in accordance with the dosing recommendations.

Table 1: Dose reduction schedule

Dose reduction schedule (Starting dose is 3.6 mg/kg)	Dose to be administered
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Haematological:

Table 2: Dose modification guidelines for thrombocytopenia

Platelets ($x10^9$/L)	
25 to < 50	Do not administer trastuzumab emtansine until platelet count recovers to ≥ 75 x 10^9/L. No dose modification is required.
< 25	Do not administer trastuzumab emtansine until platelet count recovers to ≥ 75 x 10^9/L and then dose reduce (see table 1).

Renal and Hepatic Impairment:

Table 3. Recommended dose modification for trastuzumab in patients with renal or hepatic impairment

Renal impairment		Hepatic impairment	
Mild	No adjustment to the starting dose required	Mild	No adjustment to the starting dose required
Moderate		Moderate	
The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data and therefore patients with severe renal impairment should be monitored carefully		. Trastuzumab emtansine was not studied in patients with severe hepatic impairment. Treatment of patients with hepatic impairment should be undertaken with caution due to known hepatotoxicity observed with trastuzumab emtansine (see table 4 and table 5)	

Management of adverse events:

Table 4: Dose modification guidelines for increased transaminases (AST/ALT)

Grade 2 (> 2.5 to ≤ 5 × ULN)	Grade 3 (> 5 to ≤ 20 × ULN)	Grade 4 (> 20 × ULN)
No dose modification	Do not administer trastuzumab emtansine until AST/ALT recovers to Grade ≤ 2, and then dose reduce (see table 1).	Discontinue trastuzumab emtansine.

Table 5: Dose modification guidelines for hyperbilirubinaemia

Grade 2 (> 1.5 to ≤ 3 × ULN)	Grade 3 (> 3 to ≤ 10 × ULN)	Grade 4 (> 20 × ULN)
Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1. No dose modification is required.	Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1 and then dose reduce (see table 1).	Discontinue trastuzumab emtansine.

Left Ventricular Dysfunction:

Table 6: Dose modifications for left ventricular dysfunction

LVEF < 40%	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue trastuzumab emtansine.
LVEF > 45%	Continue treatment with trastuzumab emtansine.
LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.
LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue trastuzumab emtansine.
Symptomatic CHF	Discontinue trastuzumab emtansine.

Table 7: Dose modification schedule based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Grade ≥ 3 Peripheral neuropathy		Temporarily discontinue treatment until resolution to ≤ Grade 2. At retreatment a dose reduction may be considered according to the dose reduction schedule (Table 1).
NCI-CTCAE Grade 4 hypersensitivity reactions	Discontinue	

SUPPORTIVE CARE:

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

PREMEDICATIONS:
Not usually required .

OTHER SUPPORTIVE CARE：No specific recommendations.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Cardiac toxicity:** Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. LVEF < 40% has been observed in patients treated with trastuzumab emtansine, and therefore symptomatic congestive heart failure (CHF) is a potential risk. General risk factors for a cardiac event and those identified in adjuvant breast cancer studies with trastuzumab therapy include advancing age (> 50 years), low baseline LVEF values (< 55%), low LVEF levels prior to or following the use of paclitaxel in the adjuvant setting, prior or concomitant use of antihypertensive medicinal products, previous therapy with an anthracycline and high BMI (> 25 kg/m^2). Standard cardiac function testing (echocardiogram or multigated acquisition (MUGA) scanning) should be performed prior to initiation and at regular intervals (e.g. every three months) during treatment. The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction.
- **Administration-related reactions (ARRs):** Trastuzumab emtansine treatment has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR) or hypersensitivity; treatment is not recommended for these patients. Patients should be observed closely for ARRs, especially during the first infusion. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Treatment should be interrupted in patients with a severe IRR until signs and symptoms resolve. Consideration for re-treatment should be based on clinical assessment of the severity of the reaction. Treatment must be permanently discontinued in the event of a life threatening infusion-related reaction or true hypersensitivity reaction.
- **Pulmonary toxicity:** Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical studies with

trastuzumab emtansine. Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates. It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with ILD or pneumonitis. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events.

- **Hepatotoxicity:** Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1-4 transaminitis), has been observed during treatment with trastuzumab emtansine in clinical studies. Transaminase elevations were generally transient with peak elevation at day 8 after administration of therapy and subsequent recovery to Grade 1 or less prior to the next cycle. A cumulative effect on transaminases has also been observed (the proportion of patients with Grade 1-2 ALT/AST abnormalities increases with successive cycles).

  Patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of trastuzumab emtansine in the majority of the cases. Liver function should be monitored prior to initiation of treatment and each dose. Patients with baseline elevation of ALT (e.g. due to liver metastases) may be predisposed to liver injury with a higher risk of a Grade 3-5 hepatic event or liver function test increase. Dose reductions or discontinuation for increased serum transaminases and total bilirubin are in Table 4 &5.

DRUG INTERACTIONS:

- No formal interaction studies have been performed.
- *In vitro* metabolism studies in human liver microsomes suggest that DM1, a component of trastuzumab emtansine, is metabolised mainly by CYP3A4 and, to a lesser extent, by CYP3A5.
  - Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with trastuzumab emtansine should be avoided due to the potential for an increase in DM1 exposure and toxicity.
  - Consider an alternate medicinal product with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying trastuzumab emtansine treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is coadministered and trastuzumab emtansine treatment cannot be delayed, patients should be closely monitored for adverse reactions.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Trastuzumab emtansine L01XC14

REFERENCES:

1. Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2 -positive advanced breast cancer. N Engl J Med 2012; 367: 1783-1791.
2. Hurvitz SA, Dirix L, Kocsis J et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol 2013; 31: 1157-1163.
3. Kadcyla ®Summary of Product Characteristics Accessed August 2017 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-

_Product_Information/human/002389/WC500158593.pdf

Version	Date	Amendment	Approved By
1	15/09/2015		Prof Macon Keane
2	20/09/2017	Updated with new NCCP regimen template	Prof Macon 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/