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

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	Cycle
Trastuzumab emtansine	3.6mg/kg	IV	250ml 0.9% NaCL over 90 minutes*	Every 21 days
*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.				

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to trastuzumab emtansine 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 8.
- 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	Dose to be administered
Starting dose	3.6mg/kg
First dose reduction	3mg/kg
Second dose reduction	2.4mg/kg
Requirement for further dose reduction	Discontinue treatment

Haematological:

Table 2: Dose modification of trastuzumab emtansine for thrombocytopenia

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

Renal and Hepatic Impairment:

Table 3. Dose modification of trastuzumab emtansine in 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 of trastuzumab emtansine 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 by one level (see Table 1).	Discontinue trastuzumab emtansine.

Table 5: Dose modification of trastuzumab emtansine 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 by one level (see Table 1).	Discontinue trastuzumab emtansine.

Table 6: Dose modification of trastuzumab emtansine for Drug Induced Liver Injury (DILI)

Serum transaminase and total bilirubin level	Dose modification
Serum transaminases > 3 x ULN **and** concomitant total bilirubin > 2 x ULN	Permanently discontinue trastuzumab emtansine in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication

Left Ventricular Dysfunction:

Table 7: Dose modifications of trastuzumab emtansine for left ventricular dysfunction

LVEF	Dose modification
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 8: Dose modification of trastuzumab emtansine for adverse events

Adverse reactions	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).
Grade 4 hypersensitivity reactions	Discontinue
Interstitial lung disease (ILD)/pneumonitis (any grade)	Permanently discontinue
Nodular Regenerative Hyperplasia (NRH) of the liver	Permanently 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:

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.
- **Infusion-related reactions (IRRs):** 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 IRRs, especially during the first infusion. Infusion-related reactions (due to cytokine release), characterized by one or more of the following symptoms have been reported: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia. 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. Serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver and some with a fatal outcome due to drug-induced liver injury have been observed in patients treated with trastuzumab emtansine. NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on CT scan of the liver but with normal transaminases and no other manifestations of cirrhosis. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued. 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 and 6.

- **Haemorrhage:** Cases of haemorrhagic events, including central nervous system, respiratory and gastrointestinal haemorrhage, have been reported with trastuzumab emtansine treatment. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases, the patients had thrombocytopenia, or were also receiving anti-coagulant therapy or antiplatelet therapy; in others there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary.

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.

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.
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3. Trastuzumab emtansine (Kadcyla®) Summary of Product Characteristics EMA. Last updated: 20/01/2020. Accessed July 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/kadcyla-epar-product-information_en.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	15/09/2015		Prof Maccon Keane
2	20/09/2017	Updated with new NCCP regimen template	Prof Maccon Keane
3	21/08/2019	Updated adverse events.	Prof Maccon Keane
4	28/07/2021	Reviewed. Addition of Table 6. Updated adverse effects in Table 8, and Adverse effects (hepatotoxicity).	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.