Trastuzumab Emtansine (Kadcyla®) Early Breast Cancer Therapy - 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy	C50	00659a	ODMS 20/12/2021

* 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.

Treatment is initiated within 12 weeks of surgery and administered on day 1 of a 21 day cycle for 14 cycles unless 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 for 14 cycles
*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
- Stage T1-4/N0-3/MO Breast Cancer
- HER-2 positive residual cancer as demonstrated by an accurate and validated assay
- ECOG 0-1
- LVEF ≥ 50%
- Adequate organ function
- Completion of preoperative systemic chemotherapy and HER2-directed treatment within 12 weeks of initiation
    - The preoperative chemotherapy should have consisted of at least 6 cycles of chemotherapy with a total duration of at least 16 weeks including at least 9 weeks of trastuzumab and at least 9 weeks of taxane based therapy

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)
- Evidence of clinically evident gross residual or recurrent disease following preoperative therapy and surgery
- Grade ≥ 2 peripheral neuropathy
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- HER2 positive residual cancer as demonstrated by an accurate and validated assay
- 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 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	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 <75	Do not administer trastuzumab emtansine until platelet count recovers to ≥75x10^9/L, and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
<25	Do not administer trastuzumab emtansine until platelet count recovers to ≥75x10^9/L and then dose reduce by one level (see Table 1).

Renal and Hepatic Impairment:

Table 3: Dose modification of trastuzumab emtansine in renal or hepatic impairment

Renal impairment		Hepatic impairment	
CrCl (mL/min)	**Dose**	Child-Pugh A/B	No dose adjustment is needed
≥ 30	No dose adjustment is needed		
< 30	No need for dose adjustment is expected	Child-Pugh C	Not recommended
Haemodialysis:	No need for dose adjustment is expected	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

Transaminase	Grade 2 (>3 to ≤5×ULN)	Grade 3 (>5 to ≤20×ULN)	Grade 4 (>20×ULN)
AST	Do not administer trastuzumab emtansine until AST recovers to Grade ≤ 1, and then treat at the same dose level	Do not administer trastuzumab emtansine until AST recovers to Grade ≤ 1, and then reduce one dose level	Discontinue trastuzumab emtansine
ALT	Do not administer trastuzumab emtansine until ALT recovers to Grade ≤ 1, and then reduce one dose level	Do not administer trastuzumab emtansine until ALT recovers to Grade ≤ 1, and then reduce one dose level	Discontinue trastuzumab emtansine

Table 5: Dose modification of trastuzumab emtansine for hyperbilirubinaemia

Total Bilirubin >1 to ≤2×ULN	Total Bilirubin >2×ULN
Do not administer trastuzumab emtansine until total bilirubin recovers to ≤ 1.0 × ULN, and then reduce one dose level	Discontinue trastuzumab emtansine

Left Ventricular Dysfunction:

Table 6: Dose modifications of trastuzumab emtansine for left ventricular dysfunction

LVEF	Dose modification
<45%	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue trastuzumab emtansine
≥50%	Continue treatment with trastuzumab emtansine
45% to < 50% and decrease is ≥ 10% points from baseline	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue trastuzumab emtansine
45% to < 50% and decrease is < 10% points from baseline	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks
Symptomatic CHF	Discontinue trastuzumab emtansine

Table 7: Dose modification of trastuzumab emtansine for adverse events

Adverse reactions	Severity	Recommended dose modification
Peripheral neuropathy	Grade ≥ 3	Do not administer trastuzumab emtansine until resolution ≤ Grade 2
Drug Induced Liver Injury (DILI)	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
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue trastuzumab emtansine
Heart Failure	Symptomatic CHF, Grade 3-4 left ventricular systolic dysfunction (LVSD) or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%	Discontinue trastuzumab emtansine
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue trastuzumab emtansine
Radiotherapy-Related Pneumonitis	Grade 2 Grade 3-4	Discontinue trastuzumab emtansine if not resolving with standard treatment Discontinue trastuzumab emtansine

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). 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 emtansine 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. 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.
- **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.
- **Contraception in males and females:** Women of childbearing potential should use effective contraception while receiving trastuzumab emtansine and for 7 months following the last dose of

trastuzumab emtansine. Male patients or their female partners should also use effective contraception.

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 co-administered 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.

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Version	Date	Amendment	Approved By
1	21/12/2021		Prof Janice Walshe
2	23/02/2024	Reviewed. Updated renal and hepatic dose modifications section to align with Giraud et al 2023.	Prof Janice Walshe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.