Kadcyla®

Trastuzumab emtansine

Composition

Active substance: Trastuzumab emtansine.

Excipients: Succinic acid, sodium hydroxide, sucrose, polysorbate 20 (manufactured from genetically modified maize).

Pharmaceutical form and amount of active substance per unit

Sterile powder for concentrate for solution for infusion.

Vials containing 100 mg and 160 mg trastuzumab emtansine.

After reconstitution with 5 ml or 8 ml water for injection the concentration is 20 mg/ml.

Indications and potential uses

Metastatic breast cancer (MBC)

Kadcyla is indicated in the single-drug therapy of patients with HER2-positive, inoperable, locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

Early breast cancer (EBC)

Kadcyla is indicated as monotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease in the breast and/or lymph nodes following preoperative taxane-containing chemotherapy in combination with at least trastuzumab as HER2-targeted therapy.

Dosage and administration

In order to prevent medication errors, it is essential to check the vial labels to ensure that the drug being prepared and administered is Kadcyla (trastuzumab emtansine) and not trastuzumab.

Treatment with Kadcyla should only be conducted under the supervision of a medical specialist experienced in the management of cancer patients.

Patients treated with Kadcyla should have HER2-positive tumour status, defined as an immunohistochemistry (IHC) score of 3+ or a ratio of ≥2.0 by in situ hybridisation (ISH) or by fluorescence in situ hybridisation (FISH) assessed by a validated test.

Kadcyla requires reconstitution and dilution by a healthcare professional (see *Additional information: Instructions for handling and disposal*). The product should be administered as an intravenous infusion and not as an intravenous push or bolus injection. To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Treatment plan

The recommended dose of Kadcyla is 3.6 mg/kg as an intravenous infusion every three weeks (21-day cycle).

The starting dose should be administered as an intravenous infusion over 90 minutes. Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills or other infusion-related reactions. Closely monitor the infusion site for possible subcutaneous infiltration during drug administration (see *Warnings and precautions: Extravasation*).

Provided the prior infusions were well tolerated, subsequent Kadcyla doses can be given as 30-minute infusions. However, patients should still be observed during the infusions and for at least 30 minutes thereafter.

The rate of Kadcyla infusion should be slowed or infusion interrupted if the patient develops infusion-related symptoms (see *Warnings and precautions*). Kadcyla should be withdrawn if life-threatening infusion reactions occur.

Duration of treatment

Patients with EBC should be treated for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

Patients with MBC should be treated until disease progression or unmanageable toxicity.

Delayed or missed doses

If a planned dose of Kadcyla is missed, it should be administered as soon as possible, without waiting until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion may be administered at the rate last tolerated by the patient.

Dose modifications

Management of symptomatic adverse events may require temporary interruption, dose reduction or treatment discontinuation of Kadcyla as per guidelines provided in Tables 1&2

The Kadcyla dose should not be re-escalated after a dose reduction is made.

Table 1 Dose reduction schedule

Dose reduction schedule	**Dose level**
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 2. Kadcyla dose modification guidelines

Dose modification guidelines in EBC		
Adverse reaction	**Severity**	**Treatment modification**

Increased alanine transaminase (ALT)	**Grade2-3 (>3.0 to ≤20× ULN on day of scheduled treatment)**	**Do not administer Kadcyla until ALT improves to Grade ≤1, and then reduce one dose level.**
	Grade4 (>20× ULN at any time)	**Discontinue Kadcyla.**
Increased aspartate transaminase (AST)	**Grade2 (>3.0 to ≤5× ULN on day of scheduled treatment)**	**Do not administer Kadcyla until AST improves to Grade ≤1, and then continue treatment at same dose level.**
	Grade3 (>5 to ≤20× ULN on day of scheduled treatment)	**Do not administer Kadcyla until AST improves to Grade ≤1, and then reduce one dose level.**
	Grade4 (>20× ULN at any time)	**Discontinue Kadcyla.**
Hyperbilirubinaemia	**TBILI >1.0 to ≤2.0× ULN on day of scheduled treatment**	**Do not administer Kadcyla until total bilirubin improves to ≤1.0× ULN, and then reduce one dose level.**
	TBILI >2× ULN at any time	**Discontinue Kadcyla.**
Nodular regenerative hyperplasia (NRH)	**All grades**	**Permanently discontinue Kadcyla.**
Thrombocytopenia	**Grade 2-3 on day of scheduled treatment (25,000 to <75,000/mm^3)**	**Do not administer Kadcyla until platelet count recovers to Grade ≤1 (≥75,000/mm^3), then continue treatment at same dose level. If a patient requires 2 treatment breaks due to thrombocytopenia, dose reduction by one level should be considered.**
	Grade 4 at any time <25,000/mm^3	**Do not administer Kadcyla until platelet count recovers to Grade ≤1**

		(≥75,000/mm^3), and then reduce one dose level.
Left ventricular dysfunction	**LVEF <45%**	**Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If LVEF <45% is confirmed, discontinue Kadcyla.**
	LVEF 45% to <50% and decrease by ≥10% points from baseline*	**Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If LVEF remains <50% and has not improved to <10% points from baseline, discontinue Kadcyla.**
	LVEF 45% to <50% and decrease by <10% points from baseline*	**Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.**
	LVEF ≥50%	**Continue treatment with Kadcyla.**
Heart failure	**Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%**	**Discontinue Kadcyla.**
Peripheral neuropathy	**Grade 3-4**	**Do not administer Kadcyla until improvement to Grade ≤2.**
Pulmonary toxicity	**Interstitial lung disease (ILD) or pneumonitis**	**Permanently discontinue Kadcyla.**
Radiation pneumonitis	**Grade 2**	**Discontinue Kadcyla if not reversible with standard treatment.**
	Grade 3-4	**Discontinue Kadcyla.**

Dose modification in patients with MBC		
Adverse reaction	**Severity**	**Treatment modification**
Increased transaminase (AST/ALT)	**Grade2 (>2.5 to ≤5× ULN)**	**Continue treatment at same dose level.**
	Grade3 (>5 to ≤20× ULN)	**Do not administer Kadcyla until AST/ALT improves to Grade ≤2, and then reduce one dose level.**
	Grade4 (>20× ULN)	**Discontinue Kadcyla.**
Hyperbilirubinaemia	**Grade2 (>1.5 to ≤3× ULN)**	**Do not administer Kadcyla until total bilirubin improves to Grade ≤1, and then continue treatment at same dose level.**
	Grade3 (>3 to ≤10× ULN)	**Do not administer Kadcyla until total bilirubin improves to Grade ≤1, and then reduce one dose level.**
	Grade4 (>10× ULN)	**Discontinue Kadcyla.**
Drug-induced liver injury (DILI)	**Serum transaminases >3× ULN and concomitant total bilirubin >2× ULN**	**Permanently discontinue Kadcyla in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication.**
Thrombocytopenia	**Grade3 (25,000to <50,000/mm^3)**	**Do not administer Kadcyla until platelet count recovers to Grade ≤1 (≥75,000/mm^3), and then continue treatment at same dose level.**
	Grade4 (<25,000/mm^3)	**Do not administer Kadcyla until platelet count recovers to Grade ≤1 (≥75,000/mm^3), and then reduce one dose level.**
Left ventricular	**Symptomatic CHF**	**Discontinue Kadcyla.**

dysfunction	**LVEF <40%**	**Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, discontinue Kadcyla.**
	LVEF 40% to ≤45% and decrease by ≥10% points from baseline	**Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% points from baseline, discontinue Kadcyla.**
	LVEF 40% to ≤45% and decrease by <10% points from baseline	**Continue treatment with Kadcyla.** **Repeat LVEF assessment within 3 weeks.**
	LVEF >45%	**Continue treatment with Kadcyla.**

ALT = alanine transaminase; AST = aspartate transaminase, CHF = congestive heart failure, DILI = drug-induced liver injury; LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction, TBILI = total bilirubin, ULN = upper limit of normal

***Before starting treatment with Kadcyla.**

Special dosage instructions

Elderly patients

No adjustment of the Kadcyla dose is required in patients in the ≥65-year age group.

Paediatric patients

No safety and efficacy studies of Kadcyla have been performed in children and adolescents (<18 years) .

Renal impairment

No adjustment of the starting dose of Kadcyla is required in patients with mild or moderate renal impairment (see *Pharmacokinetics: Pharmacokinetics in special patient groups*). In the absence of adequate data it is not possible to determine the potential need for dose adjustment in patients with severe renal impairment.

Hepatic impairment

No adjustment of the starting dose is required in patients with mild or moderate hepatic impairment (see *Pharmacokinetics: Pharmacokinetics in special patient groups*).

Kadcyla has not been studied in patients with severe hepatic impairment. Treatment of patients with hepatic impairment should be undertaken with caution due to the known hepatotoxicity observed with Kadcyla (see *Warnings and precautions: Hepatotoxicity*).

Contraindications

Hypersensitivity to the active substance or any excipient.

Warnings and precautions

In patients treated with Kadcyla HER2-positive tumor status must be confirmed either by demonstrating excessive HER2 protein expression or by gene amplification.

At the last revision of this prescribing information, only limited data were available on patients treated with Kadcyla for more than two years.

Infusion-related reactions

Treatment with Kadcyla has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR). Treatment with Kadcyla is not recommended for these patients.

Infusion-related reactions, characterized by one or more of the following symptoms – flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm and tachycardia – have been observed in clinical trials of Kadcyla. These symptoms were generally not severe (see *Undesirable effects*). In most patients, these reactions resolved over the course of several hours to one day after the infusion was terminated. Kadcyla treatment should be interrupted in patients with a severe IRR. Kadcyla treatment should be permanently discontinued in the event of a life-threatening IRR (see *Dosage and administration: Dose modifications*).

Hypersensitivity reactions

Treatment with Kadcyla has not been studied in patients who had trastuzumab permanently discontinued due to hypersensitivity reactions. Treatment with Kadcyla is not recommended for these patients. Hypersensitivity reactions, including serious anaphylactoid reactions, have occurred in clinical trials in which Kadcyla was administered. Patients should be observed closely for hypersensitivity reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Pulmonary toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome in the patient concerned, have been reported in clinical trials with Kadcyla (see *Undesirable effects*). Signs and symptoms include dyspnea, cough, fatigue and pulmonary infiltrates.

It is recommended that treatment with Kadcyla be permanently discontinued in patients diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where Kadcyla should be permanently discontinued if radiation pneumonitis is

Grade ≥3 or else Grade 2 that does not respond to standard treatment (see "Dose/Administration, Dose modification"). .

Patients with dyspnea at rest due to the complications of advanced malignancy, comorbidities and/or receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary events.

Patients with interstitial lung disease or pneumonitis should not be started on treatment with Kadcyla.

Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic, transient transaminase elevations, has been observed in clinical trials. However, serious hepatobiliary disorders have also been reported, including nodular regenerative hyperplasia (NRH) of the liver and some cases with fatal outcome due to drug-induced liver injury.

Transaminases and bilirubin should be monitored before starting treatment and before each dose of Kadcyla.

Kadcyla has not been studied in patients with active viral hepatitis (HBV, HCV), HIV infection, severe uncontrolled systemic disease (with severe uncontrolled hepatobiliary disease), serum transaminases >2.5 × ULN or total bilirubin >1.5 × ULN, or INR or aPTT >1.5 × ULN. Kadcyla should be permanently discontinued in patients with serum transaminases >3 × ULN and concomitant total bilirubin >2 × ULN.

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies. NRH is a rare liver condition characterized by widespread benign transformation of the liver parenchyma into small regenerative nodules. NRH may lead to noncirrhotic portal hypertension. The diagnosis of NRH can be confirmed only by histopathology. NRH should be considered in all patients with clinical symptoms of portal hypertension, with no other manifestations of cirrhosis and with normal transaminases. NRH should also be considered in patients with cirrhosis-like changes in the liver CT. Liver biopsy should be performed in such cases. Upon diagnosis of NRH, Kadcyla treatment must be permanently discontinued.

Left ventricular dysfunction

Patients treated with Kadcyla are at increased risk of developing left ventricular dysfunction. A decrease in the left ventricular ejection fraction (LVEF) to <40% has been observed on Kadcyla. Symptomatic congestive heart failure thus represents a potential risk. None of the patients taking part in the clinical trials with Kadcyla had a documented history of myocardial infarction or unstable angina pectoris in the 6 months preceding randomization, a documented history of symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment, or LVEF <50% before treatment start. Standard tests of cardiac function (echocardiogram or multigated acquisition [MUGA] scan) should therefore be performed prior to initiation of Kadcyla therapy and at regular intervals thereafter (e.g. every three months). Specific guidelines for dose modification or treatment discontinuation are described in *Dosage/ administration: Dose modifications*.

Hemorrhage

Cases of hemorrhagic events, including central nervous system, respiratory and gastrointestinal hemorrhages, some with fatal outcome, have occurred with Kadcyla. In some cases the patients were also receiving anticoagulants or antiplatelet drugs or had thrombocytopenia; in others there were no known additional risk factors. Caution is required with these medicinal products, and more intensive monitoring should be considered if concomitant use is deemed medically necessary.

Thrombocytopenia

Thrombocytopenia, or decreased platelet count, was reported in patients receiving Kadcyla in clinical trials. The majority of these patients had Grade 1 or 2 thrombocytopenia (≥50,000/mm^3) with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (≥75,000/mm^3) by the next scheduled dose. The incidence and severity of thrombocytopenia were higher in clinical trials in Asian patients.

Patients with thrombocytopenia (≤100,000/mm^3) and patients on anticoagulant treatment should be closely monitored during treatment with Kadcyla. It is recommended that platelet counts be checked prior to each Kadcyla dose. Kadcyla has not been studied in patients with platelet counts ≤100,000/mm^3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater (<50,000/mm^3), Kadcyla must not be administered until platelet counts recover to Grade 1 (≥75,000/mm^3). See *Dosage and administration: Dose modifications* in this regard.

Neurotoxicity

Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of Kadcyla. No patient with pretreatment peripheral neuropathy ≥Grade 3 (NCI CTCAE) took part in the clinical trials of Kadcyla. Kadcyla should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to Grade ≤2. Patients should be monitored for the signs and symptoms of neurotoxicity.

Extravasation

In Kadcyla clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain or swelling at the infusion site. These reactions occurred more frequently within 24 hours of infusion. No specific treatment for Kadcyla extravasation is yet known. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

Elderly patients

In the absence of adequate data the safety and efficacy of Kadcyla in patients aged 75 years and older cannot be determined.

Impairment of fertility

No specific fertility studies have been conducted with trastuzumab emtansine. However, there is a possibility that trastuzumab emtansine may impair human fertility, based on the results of general toxicity studies with trastuzumab emtansine in animals and on the anticipated pharmacological effects of DM1 as a microtubule inhibitor.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune reaction to Kadcyla.

A total of 1243 patients from seven clinical studies were tested at multiple time points for production of anti-drug antibodies (ADA) to Kadcyla. Following Kadcyla dosing, 5.1% (63/1243) of patients tested positive for anti-Kadcyla antibodies at one or more time points. In the phase I/II studies, 6.4% (24/376) of patients tested positive for anti-Kadcyla antibodies. In the EMILIA study (TDM4370g/BO21977), anti-Kadcyla antibodies were measured in 5.2% (24/466) of patients, of whom 13 were positive for neutralising antibodies. In the KATHERINE study (BO27938), anti-Kadcyla antibodies were measured in 3.7% (15/401) of patients, of whom 5 were also positive for neutralising antibodies. Due to the low incidence of ADA, conclusions cannot be drawn on the impact of anti-Kadcyla antibodies on the pharmacokinetics, safety and efficacy of Kadcyla.

Interactions

No formal drug-drug interaction studies with Kadcyla have been conducted in humans. *In-vitro* metabolic studies in human liver microsomes indicate that the DM1 component of trastuzumab emtansine is metabolized predominantly by CYP3A4 and to a lesser extent by CYP3A5. *In vitro*, DM1 neither induces nor inhibits P450-mediated metabolism. Caution is recommended when coadministering Kadcyla and potent CYP3A inhibitors.

Pregnancy and lactation

Pregnancy

No clinical studies of Kadcyla have been conducted in pregnant women.

Trastuzumab, a component of Kadcyla, may cause fetal harm or death when administered to a pregnant woman. In the postmarketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab.

Animal studies

No animal reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine. Animal studies with maytansine, a closely related chemical compound from the same maytansinoid class as DM1, suggest that DM1, the cytotoxic microtubule inhibitor component of Kadcyla, is teratogenic and possibly embryotoxic. Following the administration of trastuzumab at doses up to 25 mg/kg in pregnant monkeys, trastuzumab crossed the placental barrier during the early and late phases of gestation. The resulting concentrations of trastuzumab in fetal blood and amniotic fluid were 33% and 25% of those present in the maternal serum but were not associated with adverse findings.

Kadcyla must not be administered in pregnancy unless clearly necessary.

If Kadcyla is administered during pregnancy or if a patient becomes pregnant during treatment, apprise the patient of the potential hazard to the fetus.

Lactation

It is not known whether Kadcyla passes into human milk. Since many medicinal products pass into human milk and Kadcyla may cause serious adverse reactions in nursing infants, women should discontinue nursing before starting treatment with Kadcyla and not nurse during treatment. Nursing may only be initiated seven months after completing treatment.

Fertility

Human data are not available on the effect of Kadcyla on fertility. Animal studies revealed toxicity in male and female reproductive organs (see "Preclinical data").

Females and males of reproductive potential, contraception

Women and female partners of male patients of childbearing potential should use an effective method of contraception during treatment with Kadcyla and for at least 7 months after the last dose of Kadcyla. Men with female partners of childbearing potential should also use an effective method of contraception during treatment with Kadcyla and for at least 7 months after the last dose of Kadcyla.

Effects on ability to drive and use machines

No studies have been performed of the effects on the ability to drive and use machines.

Kadcyla has no or negligible influence on the ability to drive and use machines. The significance of reported adverse reactions such as fatigue, headache, dizziness and blurred vision on the ability to drive or use machines is unknown. Patients experiencing symptoms of an infusion-related reaction (flushing, chills, pyrexia, dyspnoea, low blood pressure or a rapid heartbeat [tachycardia]) should be advised not to drive or use machines until the symptoms abate.

Undesirable effects

Clinical trials

The safety of Kadcyla has been studied in clinical trials in 1871 patients with locally advanced or metastatic breast cancer and in 740 patients with early breast cancer.

The adverse drug reactions (ADRs) reported in association with the administration of Kadcyla in clinical trials are listed by MedDRA system organ class, using the following frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

Infections and infestations

Very common: Urinary tract infections (11.5%; ≥Grade 3: 0.3%).

Blood and lymphatic system disorders

Very common: Thrombocytopenia (25.9%; ≥Grade 3: 7.9 %), anemia (13.3 %; ≥Grade 3: 3.0%).

Common: Neutropenia (8.1%; ≥Grade 3: 2.2%), leukopenia (5.2%, ≥Grade 3: 0.4%)..

Immune system disorders

Common: Drug hypersensitivity (2.6%; ≥Grade 3: 0.2%).

Metabolism and nutritional disorders

Very common: Hypokalemia (9.8%; ≥Grade 3: 2.0%).

Psychiatric disorders

Very common: Insomnia (12.2%; ≥Grade 3: 0.1%).

Nervous system disorders

Very common: Headache (28.2%; ≥Grade 3: 0.4%), peripheral neuropathy (24.4%; ≥Grade 3: 1.4%).

Common: Dizziness (9.5%; ≥Grade 3: 0.2%), dysgeusia (6.4%), memory impairment (1.1%).

Eye disorders

Common: Dry eye (5.3%), lacrimation increased (4.5%), vision blurred (3.9%), conjunctivitis (3.7%).

Cardiac disorders

Common: Left ventricular dysfunction (2.5%; ≥Grade 3: 0.4%).

Vascular disorders

Very common: Hemorrhage (33.2%; ≥Grade 3: 1.7%).

Common: Hypertension (6.2%; ≥Grade 3: 1.8%).

Respiratory, thoracic and mediastinal disorders

Very common: Epistaxis (23.5%; ≥Grade 3: 0.3%), cough (17.8%; ≥Grade 3: 0.1%), dyspnoea (12.0%; ≥Grade 3: 1.1%).

Uncommon: Pneumonitis (0.8%; ≥Grade 3: 0.1%).

Gastrointestinal disorders

Very common: Nausea (40.5%; ≥Grade 3: 0.7 %), constipation (21.8%; ≥Grade 3: 0.3%), vomiting (18.4%; ≥Grade 3: 0.8%), diarrhoea (17.2%; ≥Grade 3: 0.8%), dry mouth (15.3%; ≥Grade 3: 0.1%), abdominal pain (14.4%; ≥Grade 3: 0.8 %), stomatitis (15.3%; ≥Grade 3: 0.1%).

Common: Dyspepsia (7.0%; ≥Grade 3: 0.1%), gingival bleeding (3.8%)..

Hepatobiliary disorders

Very common: Increased transaminases (26.5 %; ≥Grade 3: 5.6 %).

Common: Increased blood levels of alkaline phosphatase (6.2 %; ≥Grade 3: 0.4%), blood bilirubin increased (6.4%, ≥Grade 3: 0.4%).

Uncommon: Hepatic failure (0.1%; ≥Grade 3: 0.1%), nodular regenerative hyperplasia (0.2 %; ≥Grade 3: 0.1%), portal hypertension (0.2%; ≥Grade 3: 0.1%), hepatotoxicity (0.2%, ≥Grade 3: 0.2%).

Skin and subcutaneous tissue disorders

Very common: Rash (9.2 %; ≥Grade 3: 0.2 %).

Common: Pruritus (6.3%;), alopecia (3.4%), nail disorder (2.3%), palmar-plantar erythrodysaesthesia syndrome (1.6%), urticaria (1.1%).

Musculoskeletal and connective tissue disorders

Very common: Musculoskeletal pain (34.1 %; ≥Grade 3: 1.9%), arthralgia (20.9%; ≥Grade 3: 0.5 %), myalgia (13.6%; ≥Grade 3: 0.3%).

General disorders and administration site conditions

Very common: Fatigue (40.4%; ≥Grade 3: 2.1 %), pyrexia (19.5%; ≥Grade 3: 0.2%), asthenia (11.8%; ≥Grade 3: 0.8%).

Common: Chills (8.9%). Peripheral Oedema (6.9%; ≥Grade 3: 0.1%).

Uncommon: Injection site extravasation (0.3%).

Injury, poisoning and procedural complications

Common: Infusion-related reaction (3.3%; ≥Grade 3: 0.2%).

Uncommon: Radiation pneumonitis (0.4%, ≥Grade 3: 0.1%).

Note

Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reaction via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch.

Overdosage

There is no known antidote for overdose of trastuzumab emtansine. In the event of an overdose the patient should be closely monitored. Cases of overdose on treatment with trastuzumab emtansine are known, most of which were associated with thrombocytopenia. A fatal case occurred in which the patient concerned incorrectly received 6 mg/kg trastuzumab emtansine and died approximately three weeks after the overdose. No causal relationship was established.

Properties and effects

ATC code: L01XC14

Mechanism of action and pharmacodynamics

Kadcyla – trastuzumab emtansine – is a HER2-targeted antibody-drug conjugate. It consists of the humanized anti-HER2 IgG1 antibody, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. Each trastuzumab molecule is conjugated on average to 3.5 DM1 molecules.

Conjugation of DM1 to trastuzumab makes the cytotoxin selective for tumor cells that overexpress HER2, thereby enhancing the intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2 Kadcyla undergoes receptor-mediated internalization and subsequent lysosomal degradation. This results in the release of DM1-containing cytotoxic catabolites (mainly lysine-MCC-DM1).

Kadcyla possesses the mechanisms of action of trastuzumab and DM1:

- Like trastuzumab, Kadcyla binds to extracellular domain (ECD) IV of HER2 as well as to Fcγ receptors and C1q complement. In addition, like trastuzumab, Kadcyla inhibits both the shedding of HER2 ECD and phosphoinositide-3-kinase (PI3 K) signaling, while mediating antibody-dependent cell-mediated cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2.
- DM1, the cytotoxin component of Kadcyla, binds to tubulin. By inhibiting the polymerization of tubulin, DM1 and hence Kadcyla arrest the cells in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. *In vitro* cytotoxicity assay results show that DM1 is 20 to 200 times more effective than taxanes or vinca alkaloids.
- The MCC linker limits systemic release and increases targeted delivery of DM1, as shown by the very low plasma levels of free DM1.

Clinical efficacy

Early breast cancer

KATHERINE (BO27938) was a randomised, multicentre, open-label trial of 1486 patients with HER2-positive, early breast cancer with residual invasive tumour in the breast and/or axillary lymph nodes following taxane- and trastuzumab-based therapy as part of a neoadjuvant regimen before trial enrolment. Patients with pathologically documented residual invasive disease in the breast or axillary lymph nodes after completing preoperative therapy (including, for example, at least 9 weeks of HER2-targeted therapy with trastuzumab and at least 9 weeks of taxane-based chemotherapy (or, if receiving dose-dense chemotherapy regimens, at least 6 to 8 weeks of taxane-based therapy and at least 8 weeks of trastuzumab) and a total of at least 16 weeks of systemic preoperative treatment) were eligible to participate in the study. Patients received radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumour samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥2.0 determined at a central laboratory. Patients were randomised (1:1) to receive trastuzumab or Kadcyla.

Kadcyla was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with Kadcyla or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent or unacceptable toxicity, whichever occurred first. At the time of the primary analysis, the median treatment duration with Kadcyla was 10 months (range: 1-12) and the median treatment duration with trastuzumab was 10 months (range: 1-13).

The primary efficacy endpoint of the study was invasive disease-free survival (IDFS). IDFS was defined as the time from the date of randomisation to first occurrence of ipsilateral invasive breast cancer recurrence, ipsilateral local or regional invasive breast cancer recurrence, distant metastasis, contralateral invasive breast cancer or death from any cause.

Patient demographics and baseline tumour characteristics were balanced between treatment arms. The average age was approximately 49 years (range 23-80 years), 72.8% were White, 8.7% were Asian and 2.7% were Black or African American. All but 5 patients were women. 22.5% of patients were enrolled in North America, 54.2% in Europe and 23.3% in the rest of the world. Tumour prognostic characteristics including hormone receptor status (positive: 72.3%, negative: 27.7%), clinical stage at presentation (inoperable: 25.3%, operable: 74.8%) and pathological nodal status after preoperative therapy (node-positive: 46.4%, node-negative/not evaluated: 53.6%) were similar in the study arms.

Most patients (76.9%) had received neoadjuvant chemotherapy with anthracycline. 19.5% of patients received another HER2-targeted agent in addition to trastuzumab as a component of their neoadjuvant therapy. Pertuzumab was used as the second therapy in 93.8% of patients who received a second neoadjuvant HER2-directed agent.

A statistically significant improvement in IDFS was observed in patients who received trastuzumab emtansine compared with trastuzumab (HR = 0.50, 95% CI [0.39, 0.64], $p<0.0001$). The estimated 3-year IDFS rates were 88.3% in the trastuzumab emtansine-treated arm vs 77.0% in the trastuzumab-treated arm. The prespecified subgroups analysed for IDFS were consistent with the overall results and included patients with hormone receptor-negative and/or hormone receptor-positive disease, patients who received neoadjuvant trastuzumab alone or with another HER2-targeted therapy (pertuzumab [Perjeta®] or other agents), or patients who were pathologically node-positive or node-negative/not evaluated after preoperative therapy. The other secondary endpoints were likewise consistent with the results for the primary endpoint and included a second primary non-breast cancer, disease-free survival (DFS), overall survival (OS) and distant recurrence-free interval (DRFI).

A total of 98 deaths were reported, i.e. 42 (5.7%) deaths in the trastuzumab emtansine treatment arm vs 56 (7.5%) deaths in the trastuzumab treatment arm (hazard ratio for overall survival: 0.70, 95% CI: 0.47 to 1.05; $p=0.0848$). Median follow-up was similar in both arms, i.e. 41.4 months in the trastuzumab emtansine treatment arm and 40.9 months in the trastuzumab treatment arm.

At a later data cutoff point, 116 deaths were reported, i.e. 50 (6.7%) in the trastuzumab emtansine treatment arm vs 66 (8.9%) in the trastuzumab treatment arm, with a median follow-up of 47.5 months vs 46.7 months.

Metastatic breast cancer

A randomized multicenter international open clinical Phase III study (TDM4370g/BO21977) was performed in patients with HER2-positive inoperable locally advanced breast cancer or metastatic breast cancer previously treated with trastuzumab and a taxane, including adjuvant therapy, and relapsing within six months of completing adjuvant therapy. HER2-positive disease, defined as 3+ IHC or by gene amplification using ISH, was confirmed in breast tumor samples by a central laboratory before inclusion. Patient and tumor baseline characteristics were well-balanced between the treatment groups. Patients randomized to the Kadcyla treatment group had a mean age of 53 years. Most patients were female (99.8%), white (72%) and 57% had estrogen and/or progesterone receptor-positive disease. The study compared safety and efficacy between Kadcyla and lapatinib plus capecitabine. Treatment with Kadcyla or lapatinib plus capecitabine was allocated as follows among the 991 randomized patients:

- Kadcyla arm: Kadcyla 3.6 mg/kg intravenously (i.v.) over 30−90 minutes on Day 1 of a 21-day cycle.
- Control arm (lapatinib plus capecitabine): lapatinib 1250 mg/day orally once per day of a 21-day cycle plus capecitabine 1000 mg/m^2 orally twice daily on Days 1–14 of a 21-day cycle.

The co-primary efficacy endpoints of the study were progression-free survival (PFS), assessed by an independent review committee (IRC), overall survival (OS) and survival rates at specified intervals (after 1 year and 2 years).

The clinical trials also determined time to symptom progression, defined by a decrease of 5 points in the Trials Outcome Index-Breast (TOI-B) subscale score of the Functional Assessment of Cancer Therapy-Breast Quality of Life (FACT-B QoL) questionnaire. A 5-point change in the TOI-B is considered clinically significant.

Table 3 Summary of efficacy data from study TDM4370g/BO21977 (EMILIA)

	Lapatinib + capecitabine n=496	**Trastuzumab-emtansine n=495**
Primary endpoints		
PFS (IRC assessment)		
Number (%) of patients with event	304 (61.3%)	265 (53.5%)
Median duration of PFS (months)	6.4	9.6
Hazard ratio (stratified*)	0.650	
95% CI for hazard ratio	(0.549, 0.771)	
p-value (log-rank test, stratified*)	<0.0001	
OS (interim analysis) **		
Number (%) of patients who died	182 (36.7%)	149 (30.1%)
Median duration of survival (months)	25.1	30.9
Hazard ratio (stratified*)	0.682	
95% CI for hazard ratio	(0.548, 0.849)	
p-value (log-rank test*)	0.0006	

1-year survival rate (95% CI)	78.4% (74.62, 82.26)	85.2% (81.99, 88.49)
2-year survival rate (95% CI)	51.8% (45.92, 57.73)	64.7% (59.31, 70.19)
Central secondary endpoints		
PFS (investigator assessment)		
Number (%) of patients with event	335 (67.5%)	287 (58.0%)
Median duration of PFS (months)	5.8	9.4
Hazard ratio (95% CI) p-value (log-rank test*)	0.658 (0.560, 0.774) <0.0001	
Objective response rate		
Patients with measurable disease	**389**	**397**
Number of patients with OR (%)	120 (30.8%)	173 (43.6%)
Difference (95% CI); p-value (Mantel-Haenszel chi-squared test*)	12,7% (6.0%, 19.4%) 0.0002	
Duration of objective response (months)		
Number of patients with OR	120	173
Median 95% CI	6.5 (5.45, 7.16)	12.6 (8.38, 20.76)
Time to symptom progression		
Number of evaluable patients	445	450
Number (%) of patients with event	257 (57.5%)	246 (54.7%)
Median time to event (months)	4.6	7.1
Hazard ratio, 95% CI p-value (log-rank test*)	0.796 (0.667, 0.951) 0.0121	

PFS: progression-free survival; OS: overall survival; OR: objective response.

* Stratified by: world region (USA, Western Europe, other), number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0–1 vs >1) and visceral vs nonvisceral disease.

** The first interim analysis for OS was conducted at the time of the primary PFS analysis. It identified a strong treatment-related effect not exceeding the prespecified efficacy stopping boundary. A second interim analysis for OS (results in this table) was conducted when 331 OS events were observed.

A treatment benefit was observed in the subpopulation of patients without prior systemic cancer therapy for metastatic disease (n=118); the hazard ratio values for PFS and OS were 0.51 (95% CI: 0.30; 0.85) and 0.61 (95% CI: 0.32; 1.16). Median PFS in the Kadcyla group was 10.8 months whereas median OS was not reached. In the group treated with lapatinib and capecitabine median PFS was 5.7 months and median OS 27.9 months.

A randomized multicenter open Phase II study (TDM4450g/BO21976) compared the effects of Kadcyla to trastuzumab plus docetaxel in patients with HER2-positive MBC who had received no prior chemotherapy for the treatment of metastases. Patients were randomized to 3.6 mg/kg Kadcyla i.v. every three weeks (n=67) or a loading dose of 8 mg/kg trastuzumab i.v., followed by 6 mg/kg i.v. every three weeks, plus 75–100 mg/m^2 docetaxel i.v. every three weeks (n=70).

The primary endpoint was investigator-assessed PFS. Median PFS was 9.2 months in the trastuzumab plus docetaxel treatment arm and 14.2 months in the Kadcyla treatment arm (hazard ratio, 0.59; p=0.035) with a median follow-up of approximately 14 months in both arms. The overall response rate (ORR) was 58.0% with trastuzumab plus docetaxel and 64.2% with Kadcyla. Median duration of response was not reached with Kadcyla and was 9.5 months in the control arm.

A clinical data cutoff date of 31 August 2011 was set for the analysis of OS in study TDM4450b/BO21976. Median follow-up was 12.9 months in the trastuzumab emtansine arm, and 12.4 months in the trastuzumab plus docetaxel arm. Few patients (13) had died at this point in either treatment arm and OS rates were similar in both arms (HR=1.06; 95% CI: 0.477; 2.352). The OS results should be viewed with caution due to the few deaths and the fact that 50% of the patients randomized to the trastuzumab plus docetaxel arm switched to the trastuzumab emtansine group after confirmation of progressive disease (PD). In addition, a substantial fraction (>50%) of all patients received at least one subsequent cancer treatment after progression of their disease. Time to a decrease in FACT-B TOI score was longer in the Kadcyla arm than in the control arm (median times to symptom progression: 7.5 months vs 3.5 months, respectively; hazard ratio, 0.58; p=0.022).

A single-arm open Phase II trial (TDM4374g) studied the effects of Kadcyla in patients with HER2-positive incurable locally advanced cancer or MBC. All patients had received prior HER2-specific treatments (trastuzumab and lapatinib) and chemotherapy (anthracycline, taxane and capecitabine) as neoadjuvant or adjuvant therapy or for locally advanced or metastatic disease. The median number of cancer drugs per background disease was 8.5 (range: 5 to 19), while patients with metastatic disease received a median number of 7.0 cancer drugs (range: 3 to 17), including all drugs designed for the treatment of breast cancer.

Patients (n=110) received 3.6 mg/kg Kadcyla intravenously every three weeks until the onset of disease progression or unacceptable toxicity.

The primary efficacy analyses were ORR, based on independent radiologist assessment, and duration of objective response. According to the IRC and investigator assessments, ORR was 32.7% (95% CI: 24.1, 42.1), i.e. n=36 responders. IRC median duration of response was not reached (95% CI, 4.6 months to non-determinable).

Pharmacokinetics

The population pharmacokinetic analysis of trastuzumab emtansine suggested no difference in Kadcyla exposure based on disease status (adjuvant vs metastatic setting).

Absorption

Kadcyla is administered intravenously. No studies have been conducted with other routes of administration.

Distribution

When administered intravenously every three weeks, Kadcyla displays linear pharmacokinetics in the dose range 2.4 to 4.8 mg/kg. Clearance was faster in patients receiving a dose of 1.2 mg/kg or less.

In patients in study TDM4370g/BO21977 and in study BO29738 receiving 3.6 mg/kg Kadcyla intravenously every three weeks, the mean maximum serum concentration (C_{max}) of trastuzumab emtansine in cycle 1 was 83.4 (±16.5) µg/ml and 72.6 (± 24.3) µg/ml, respectively. Based on population pharmacokinetic analysis after intravenous dosing, the central volume of distribution of trastuzumab emtansine was 3.13 l, thus approximating to the plasma volume.

In vitro, the mean binding of DM1 to human plasma proteins was 93%. DM1 is a substrate of P-gp. Even at the highest tested concentration of 369 ng/ml, DM1 does not inhibit P-gp activity *in vitro*.

Metabolism

Kadcyla is believed to be degraded by proteolysis in cell lysosomes without major involvement of cytochrome P450 isoenzymes. The degradation products, including Lys-MCC-DM1, MCC-DM1 and DM1, are detectable in human plasma at low concentrations. In study TDM4370g/BO21977 and in study BO29738,mean maximum DM1 concentrations in Cycle 1 after Kadcyla administration were consistently low at a mean of 4.61 (± 1.61 ng/ml) and 4.71 (± 2.25) ng/ml, respectively.

In vitro, metabolic studies in human hepatic microsomes support the conclusion that the DM1 component of trastuzumab emtansine is metabolized mainly by CYP3A4 and to a lesser degree by CYP3A5.

Elimination

Based on population pharmacokinetic (PK) analysis, following intravenous infusion of Kadcyla in patients with HER2-positive metastatic breast cancer, clearance of Kadcyla was 0.68 l/day and the elimination half-life ($t_{½}$) approximately four days. No accumulation of Kadcyla was observed after repeated dosing of intravenous infusion every three weeks.

Based on population PK analysis, body weight, albumin, the sum of longest diameter of target lesions by RECIST (Response Evaluation Criteria in Solid Tumors), HER2 extracellular domain (ECD) shedding, baseline trastuzumab concentrations and AST were identified as statistically significant covariates for the PK parameters of trastuzumab emtansine. However, the magnitude of the effect of these covariates on trastuzumab emtansine exposure argues against a clinically meaningful effect on Kadcyla exposure. In nonclinical studies trastuzumab emtansine degradation products, including DM1, Lys-MCC-DM1 and MCC-DM1, were excreted mainly in bile, with minimal excretion in urine.

Pharmacokinetics in special patient groups

Population pharmacokinetic analysis of Kadcyla revealed no evidence of an effect of race. As most patients in the clinical trials of Kadcyla were women, the effect of sex on the pharmacokinetics of Kadcyla has not been formally evaluated.

Elderly patients

Population pharmacokinetic analysis of Kadcyla revealed no evidence of an effect of age. No significant difference was found in the pharmacokinetics of Kadcyla between patients in the age groups <65 years (n=577), 65–75 years (n=78) and >75 years (n=16).

Patients with renal impairment

Population pharmacokinetic analysis of Kadcyla revealed no evidence of an effect of creatinine clearance. The pharmacokinetic parameters of Kadcyla in patients with renal impairment, whether mild (creatinine clearance [CrCl] 60–89 ml/min, n=254) or moderate (CrCl 30–59 ml/min, n=53), were similar to those in patients with normal renal function (CrCl ≥90 ml/min, n=361). Pharmacokinetic data in patients with severe renal impairment (CrCl 15–29 ml/min) are limited (n=1), with the result that no dose recommendations can be given.

Hepatic impairment

The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of Kadcyla to metastatic HER2-positive breast cancer patients with normal hepatic function (n=10) and mild (Child-Pugh A; n=10) or moderate (Child-Pugh B; n=8) hepatic impairment.

–Plasma concentrations of DM1 and DM1-containing catabolites (Lys-MCC-DM1 and MCC-DM1) were low and comparable between patients with and without hepatic impairment.

–Systemic exposures (AUC) of trastuzumab emtansine at Cycle 1 in patients with mild and moderate hepatic impairment were approximately 38% and 67% lower than in patients with normal hepatic function, respectively. Trastuzumab emtansine exposure (AUC) at Cycle 3 after repeated dosing in patients with mild (n=8) or moderate (n=3) hepatic impairment was within the range observed in patients with normal (n=9) hepatic function.

Kadcyla has not been studied in patients with severe hepatic impairment (Child-Pugh class C). No pharmacokinetic study has been conducted and no population PK data have been collected in patients with severe hepatic impairment (Child-Pugh class C).

Preclinical data

Mutagenicity and carcinogenicity

No carcinogenicity studies have been performed to determine the carcinogenic potential of Kadcyla.

DM1 was not mutagenic in an *in vitro* bacterial reverse mutation assay. An *in vivo* bone marrow micronucleus assay with trastuzumab emtansine in cynomolgus monkeys showed no evidence of chromosomal damage. However, a bone marrow micronucleus assay in

rats given a single low dose of DM1 within the concentration range found in humans after the administration of trastuzumab emtansine showed the development of micronuclei, thus confirming that Kadcyla has aneugenic and/or clastogenic activity.

There have been no carcinogenicity studies of trastuzumab emtansine.

Reproductive toxicity

No fertility studies in animals have been performed to evaluate the effect of Kadcyla. . Developmental toxicity has been observed in the clinical background with the administration of trastuzumab. In addition, maytansine has been associated with developmental toxicity in nonclinical studies, suggesting that DM1, the microtubule inhibitor maytansinoid cytotoxin component of trastuzumab emtansine, has similar teratogenic and potentially embryotoxic activity.

Based on results from animal toxicity studies, Kadcyla may impair fertility in humans. In a single-dose toxicity study of trastuzumab emtansine in rats, degeneration of seminiferous tubules with hemorrhage in the testes associated with increased weights of testes and epididymides at a severely toxic dose level (60 mg/kg; about 4 times the clinical exposure based on AUC) were observed. The same dose in female rats resulted in signs of hemorrhage and necrosis of the corpus luteum in ovaries. In monkeys dosed with trastuzumab emtansine once every three weeks for 12 weeks (four doses), at up to 30 mg/kg (about 7 times the clinical exposure based on AUC), there were decreases in the weights of epididymides, prostate, testes, seminal vesicles and uterus, although the interpretation of these effects is unclear due to the varied sexual maturity of enrolled animals.

Additional information

Incompatibilities

Do not use (5%) dextrose solution as it causes the protein to aggregate.

Do not mix or dilute Kadcyla with other medicinal products.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Stability of the reconstituted solution

The solution reconstituted with water for injection should be used immediately. If necessary, the reconstituted vials can be stored for up to 24 hours at 2–8°C but must be discarded thereafter.

Do not freeze the reconstituted solution.

Stability of the infusion solution containing the reconstituted product

Once diluted in polyvinylchloride (PVC) bags or latex- and PVC-free polyolefin bags with 0.9% or 0.45% sodium chloride solution for injection, the reconstituted trastuzumab emtansine solution may be stored before use for up to 24 hours at 2–8°C. Since particulates may form on storage after dilution in 0.9% sodium chloride solution for injection, a 0.2 µm or 0.22 µm in-line (polyethersulfone, PES) filter is required for administration.

Do not freeze the solution for infusion containing the reconstituted product.

Special storage instructions

Store in a refrigerator (2–8°C).

Keep out of reach of children.

Instructions for handling and disposal

Proceed using appropriate aseptic technique. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.

The reconstituted product contains no preservative and is intended for single use only. Discard any residual unused product.

- Using a sterile syringe, slowly inject 5 ml of sterile water for injection into the 100 mg vial of trastuzumab emtansine or 8 ml of sterile water for injection into the 160 mg vial.
- Swirl the vial gently until the contents have fully dissolved. DO NOT SHAKE!
- Store the reconstituted trastuzumab emtansine solution at 2–8°C; discard unused trastuzumab emtansine after 24 hours.

Before administration inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be free of visible particulates and clear to slightly opalescent. The reconstituted solution should be colorless to pale brown. Do not use if the reconstituted solution contains visible particulates or is cloudy or discolored.

Dilution instructions

Determine the solution volume required based on a dose of 3.6 mg trastuzumab emtansine per kg of body weight (see *Dosage and administration: Table 1 Dose reduction schedule*):

$$\textbf{Volume}\ (\text{ml}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\text{mg/kg})}{\textbf{20}\ \text{mg/ml (concentration of reconstituted solution)}}$$

Withdraw the corresponding volume of solution from the vial and add it to an infusion bag containing 250 ml of 0.45% or 0.9% sodium chloride. Do not use (5%) dextrose solution. If using 0.45% sodium chloride, there is no need to interpose a 0.2 µm or 0.22 µm polyethersulfone (PES) filter. If using 0.9% sodium chloride solution for the infusion, a 0.2 µm or 0.22 µm PES in-line filter is required. Once prepared, the infusion should be administered immediately. If not administered immediately, it may be stored in the refrigerator at 2–8°C for up to 24 hours. The solution for infusion must be neither frozen nor shaken during storage.

Disposal of unused and expired medicinal product

Any medicinal products unused/expired after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Packs

Vials 100 mg	1
Vials 160 mg	1

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at November 2019

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland by
Patheon Manufacturing Services LLC, NC, USA