NOVARTIS

TYKERB® (lapatinib)

250 mg tablet

Professional Information

Document status: Final

Release date: 14 September 2018

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

TYKERB® Tablets

COMPOSITION:

Each film-coated tablet contains lapatinib ditosylate monohydrate equivalent to 250 mg lapatinib.

The excipients include microcrystalline cellulose, povidone, sodium starch glycolate and magnesium stearate.

The film-coat consists of hypromellose, titanium dioxide, macrogol/PEG 400, polysorbate 80, iron oxide yellow and iron oxide red.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Lapatinib is an inhibitor with reversible and selective inhibition of the intracellular tyrosine kinase domains of both EGFR (ErbB1) and of HER2+/neu (ErbB2+) receptors (estimated Ki^{app} values of 3 nM and 13 nM, respectively) with a slow off-rate from these receptors (half-life greater than or equal to 300 minutes). Lapatinib inhibits ErbB-driven tumour cell growth *in vitro* and in various animal models.

Randomised trials in hormone-sensitive metastatic breast cancer indicate that a HER2 or EGFR tyrosine kinase inhibitor may improve PFS when added to endocrine therapy.

Cardiac electrophysiology

QT Prolongation

Study EGF114271: The effect of lapatinib on the QT-interval was evaluated in a single-blind, placebo-controlled, single sequence (placebo and active treatment) crossover study in patients with advanced solid tumors (N=58). During the 4-day treatment period, three doses of matching placebo were administered 12 hours apart in the morning and evening on Day 1 and in the morning on Day 2. This was followed by three doses of lapatinib 2000 mg administered in the same way. Measurements, including ECGs and pharmacokinetic samples were done at baseline and at the same time points on Day 2 and Day 4.

In the evaluable population (N=37), the maximum mean ΔΔQTcF (90 % CI) of 8.75 ms (4.08, 13.42) was observed 10 hours after ingestion of the third dose of lapatinib 2000 mg. The ΔΔQTcF exceeded the 5 ms threshold and the upper bound 90 % CIs exceeded the 10 ms threshold at multiple time points. The results for the pharmacodynamic population (n=52) were consistent with those from the evaluable population (maximum ΔΔQTcF (90 % CI) of 7.91 ms (4.13, 11.68) observed 10 hours after ingestion of the third dose of lapatinib. The pharmacokinetic/pharmacodynamic analyses confirmed the presence of a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.

Pharmacokinetic properties:

Absorption: Absorption following oral administration of lapatinib is incomplete and variable (approximately 50 to 100 % coefficient of variation in AUC). Serum concentrations appear after a median lag time of 0,25 hours (range 0 to 1,5 hours). Peak plasma concentrations (C_{max}) of

lapatinib are achieved approximately 4 hours after administration. Daily dosing of 1 250 mg produces steady state geometric mean (95 % confidence interval) C_{max} values of 2,43 (1,57 to 3,77) µg/ml and AUC values of 36,2 (23,4 to 56) µg.hr/ml.

Systemic exposure to lapatinib is increased when administered with food. Lapatinib AUC values were approximately 3- and 4-fold higher (C_{max} approximately 2,5 and 3-fold higher) when administered with a low fat (5 % fat [500 calories]) or with a high fat (50 % fat [1 000 calories]) meal, respectively.

Distribution**:** Lapatinib is highly bound (greater than 99 %) to albumin and alpha-1 acid glycoprotein. *In vitro* studies indicate that lapatinib is a substrate for the transporters BCRP (ABCG1) and p-glycoprotein (Pgp) (ABCB1). Lapatinib has also been shown to inhibit Pgp (IC_{50} 2,3 µg/ml, BCRP (IC_{50} 0,014 µg/ml) and the hepatic uptake transporter OATP181 (IC_{50} 2,3 µg/ml), *in vitro* at clinically relevant concentrations. The clinical significance of these effects on the pharmacokinetics of other medicines or the pharmacological activity of other anti-cancer agents is not known.

Lapatinib does not significantly inhibit the organic anion transporter (OAT) or organic cation transporter (OCT) renal transporters (*in vitro* IC_{50} values were greater than or equal to 6,9 µg/ml).

Metabolism**:** Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which account for more than 14 % of the dose recovered in the faeces or 10 % of lapatinib concentration in plasma.

Lapatinib inhibits CYP3A (Ki 0,6 to 2,3 µg/ml) and CYP2C8 (0,3 µg/ml) *in vitro* at clinically relevant concentrations. Lapatinib did not significantly inhibit the following enzymes in human

liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes (*in vitro* IC_{50} values were greater than or equal to 6,9 µg/ml).

In healthy volunteers receiving ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure to lapatinib was increased approximately 3,6-fold, and half-life increased 1,7-fold.

In healthy volunteers receiving carbamazepine, a CYP3A4 inducer, at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure to lapatinib was decreased approximately 72 %.

***Elimination*:** The half-life of lapatinib measured after single doses increases with increasing dose.

However, daily dosing of lapatinib results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours.

Lapatinib is predominantly eliminated through metabolism by CYP3A4/5. The primary route of elimination for lapatinib and its metabolites is in faeces, with less than 2 % of the dose (as lapatinib and metabolites) excreted in urine. Recovery of lapatinib in faeces accounts for a median 27 % (range 3 to 67 %) of an oral dose.

Special Patient Populations:

Renal Impairment:

Lapatinib pharmacokinetic properties have not been studied in patients with renal impairment or in patients undergoing haemodialysis. However, less than 2 % of an administered dose (as unchanged lapatinib and metabolites) is eliminated by the kidneys.

Hepatic Impairment:

There is limited information on the clinical use of lapatinib in patients with hepatic impairment. The pharmacokinetics of lapatinib were examined in subjects with moderate (n=8) or severe (n=4) hepatic impairment (Child-Pugh scores of 7 - 9, or greater than 9, respectively) and in 8 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100 mg dose increased approximately 56 % and 85 % in subjects with moderate and severe hepatic impairment, respectively. Administration of lapatinib in patients with hepatic impairment should be undertaken with caution due to increased exposure to the medicine. In patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued and patients should not be retreated with lapatinib (see **DOSAGE AND DIRECTIONS FOR USE** and **WARNINGS AND SPECIAL PRECAUTIONS**).

INDICATIONS:

HER2+ over expressing metastatic breast cancer:

- TYKERB, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress HER2+/neu (ErbB2+) and who have progressed on prior therapy including trastuzumab therapy in the metastatic setting.
- TYKERB in combination with paclitaxel, is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2+/neu (Erb2).

Hormone-sensitive metastatic breast cancer:

TYKERB ·in combination with an aromatase inhibitor is indicated for the treatment of patients with hormone-sensitive metastatic breast cancer whose tumours overexpress HER2+/neu (ErbB2+).

CONTRA-INDICATIONS:

TYKERB is contra-indicated in patients with hypersensitivity to any of the ingredients (see **SIDE EFFECTS**).

Please refer to the capecitabine prescribing information for relevant contra-indications and safety information when administering TYKERB in combination with capecitabine.

Moderate to severe hepatic impairment.

WARNINGS AND SPECIAL PRECAUTIONS:

Diarrhoea (58 - 65 %) (all grades), including severe diarrhoea (10 - 14 %) (grade 3-4), has been reported with TYKERB treatment (see SIDE EFFECTS). Early identification and intervention is critical for the optimal management of diarrhoea. Patients should be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhoea with anti-diarrhoeal agents after the first unformed stool is recommended.

Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids and interruption or discontinuation of TYKERB therapy (see **Dosage and Directions for USE - dose delay and dose reduction - other toxicities).**

Cardiac Toxicity: TYKERB has been associated with reports of decreases in left ventricular ejection fraction [LVEF] (see SIDE EFFECTS). Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with lapatinib to ensure that the patient has a baseline LVEF that is within the institutions normal limits. LVEF should continue to be evaluated during treatment with lapatinib to ensure that LVEF does not decline to an unacceptable level (see Dosage and Directions for USE - dose delay and dose reduction - cardiac events).

A concentration dependent increase of the QTc interval has been observed in a dedicated placebo-controlled crossover study in subjects with advanced solid tumors (*see* **PHARMACOLOGICAL ACTIONS**). Caution should be taken if lapatinib is administered to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation. Hypokalemia, hypocalcaemia or hypomagnesemia should be corrected prior to lapatinib administration.

Interstitial Lung Disease and Pneumonitis: TYKERB has been associated with reports of interstitial lung disease and pneumonitis (see **SIDE EFFECTS**). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis (see **DOSAGE AND DIRECTIONS FOR USE**).

Hepatotoxicity: Hepatotoxicity (ALT or AST > 3 times the upper limit of normal and total bilirubin > 1,5 times the upper limit of normal) has been observed in clinical trials and post-marketing experience. The hepatotoxicity may be severe and deaths have been reported. The hepatotoxicity may occur days to several months after initiation of TYKERB. Liver

function tests (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment, every 4 to 6 weeks during treatment and as clinically indicated. If changes in liver function are severe, therapy with TYKERB should be discontinued and patients should not be retreated with TYKERB (see **SIDE EFFECTS** and **DOSAGE AND DIRECTIONS FOR USE**).

TYKERB is contra-indicated in patients with moderate to severe pre-existing hepatic impairment (see **DOSAGE AND DIRECTIONS FOR USE**).

In patients who develop hepatotoxicity while on therapy, TYKERB should be discontinued and patients should not be retreated with TYKERB (see **DOSAGE AND DIRECTIONS FOR USE** and ***Pharmacokinetic properties* - Special Patient Populations**).

Severe cutaneous reactions: Severe cutaneous reactions have been reported with lapatinib. If erythema multiforme or life-threatening reactions such as, Stevens-Johnson syndrome, or toxic epidermal necrolysis (e.g. progressive skin rash often with blisters or mucosal lesions) are suspected, discontinue treatment with lapatinib (see **DOSAGE AND DIRECTIONS FOR USE**).

Concomitant Treatment with Inhibitors or Inducers of CYP3A4: Concomitant treatment with inhibitors or inducers of CYP3A4 should proceed with caution due to risk of increased or decreased exposure to lapatinib, respectively (see **INTERACTIONS**).

Ability to perform tasks that require judgement, motor or cognitive skills:

The clinical status of the patient and the adverse event profile of TYKERB should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should be advised to refrain from these activities until the effect of treatment with TYKERB on the above skills becomes clear.

INTERACTIONS:

Lapatinib is predominantly metabolised by CYP3A (see ***Pharmacokinetic properties***). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetic properties of lapatinib.

Co-administration of lapatinib with known inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole or grapefruit) should proceed with caution and clinical response and adverse events should be carefully monitored (see **WARNINGS AND SPECIAL PRECAUTIONS**). If a strong CYP3A4 inhibitor must be administered to patients, based on pharmacokinetic studies, a dose reduction of 500 mg/day of TYKERB is predicted to adjust the lapatinib AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately one week should be allowed before the TYKERB dose is adjusted upward to the indicated dose.

Co-administration of lapatinib with known inducers of CYP3A4 (e.g. rifampin, carbamazepine, or phenytoin) should proceed with caution and clinical response and adverse events should be carefully monitored (see **WARNINGS AND SPECIAL PRECAUTIONS**). If a strong CYP3A4 inducer must be administered to patients, based on pharmacokinetic studies, the dose of TYKERB should be gradually titrated from 1 250 mg/day up to 4 500 mg/day, based on tolerability. This dose of TYKERB is predicted to adjust the lapatinib AUC to the range observed without inducers and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, the TYKERB dose should be reduced over approximately 2 weeks to the indicated dose.

Pre-treatment with a proton pump inhibitor (esomeprazole) decreases lapatinib exposure by an average of 27 %. This effect decreases with increasing age from approximately 40 to 60 years. Therefore, caution should be advised when TYKERB is used in patients pre-treated with a proton pump inhibitor.

Lapatinib inhibits CYP3A4 in vitro at clinically relevant concentrations. Co-administration of TYKERB with orally administered midazolam resulted in an approximate 45 % increase in the AUC of midazolam. There was no meaningful increase (14 %) in AUC when midazolam was administered intravenously. Caution should be exercised when dosing TYKERB concurrently with orally administered medications with narrow therapeutic windows that are substrates of CYP3A4 (see ***Pharmacokinetic properties****).*

Lapatinib inhibits CYP2C8 *in vitro* at clinically relevant concentrations. Caution should be exercised when dosing TYKERB concurrently with medications with narrow therapeutic windows (e.g. paclitaxel, torsemide, repaglinide) that are Substrates of CYP2C8 (see ***Pharmacokinetic properties***).

Co-administration of TYKERB with intravenous paclitaxel increased the exposure of paclitaxel by 23 % due to lapatinib inhibition of CYP2C8 and/or P-glycoprotein (Pgp). An increase in the incidence and severity of diarrhoea and neutropenia has been observed with this combination in clinical trials. Caution is advised if TYKERB is co-administered with paclitaxel.

Co-administration of TYKERB with intravenously administered docetaxel did not significantly affect the AUC or Cmax of either active substance. However the occurrence of docetaxel-induced neutropaenia was increased.

Co-administration of TYKERB with irinotecan (when administered as part of the FOLFIRI regimen) resulted in an approximate 40 % increase in the AUC of SN-38, the active metabolite of irinotecan. The precise mechanism of this interaction is unknown. Caution is advised if TYKERB is co-administered with irinotecan.

Lapatinib is a substrate for the transport protein Pgp and BCRP (Breast Cancer Resistant Protein). Inhibitors and inducers of these proteins may alter the exposure and/or distribution of lapatinib (see ***Pharmacokinetic properties***).

Lapatinib inhibits the transport protein Pgp *in vitro* at clinically relevant concentrations. Co-administration with orally administered digoxin resulted in an appropriate 98 % increase in AUC of digoxin. Caution should be exercised when dosing TYKERB concurrently with medicines with narrow therapeutic windows that are substrates of Pgb.

Lapatinib inhibits the transport proteins BCRP and OAT1B1 *in vitro*. The clinical relevance of this effect has not been evaluated. It cannot be excluded that lapatinib will affect the pharmacokinetics of substrates of BCRP (e.g. topotecan) and OATP1B1 (e.g. rosuvastatin) (see ***Pharmacokinetic properties***).

Lapatinib does not significantly inhibit the organic anion transporter (OAT) or organic cation transporter (OCT) renal transporters (*in vitro* IC_{50} values were greater than or equal to 6,9 ug/ml).

Concomitant administration of TYKERB with capecitabine, letrozole or trastuzumab did not meaningfully alter the pharmacokinetic properties of these agents (or the metabolites of capecitabine) or lapatinib.

The bioavailability of lapatinib is affected by food (see **DOSAGE AND DIRECTIONS FOR USE** and ***Pharmacokinetic properties***).

PREGNANCY AND LACTATION:

Pregnancy: Safety in pregnancy has not been established. The effect of TYKERB on human pregnancy is unknown. Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with TYKERB.

Lapatinib was not teratogenic when studied in pregnant rats and rabbits but caused minor abnormalities at doses which were maternally toxic.

Lactation: It is not known whether lapatinib is excreted in human milk. Women who are receiving therapy with TYKERB should not breastfeed their babies.

DOSAGE AND DIRECTIONS FOR USE:

TYKERB treatment should only be initiated by a medical practitioner experienced in the administration of anti-cancer agents.

Prior to the initiation of treatment, left ventricular ejection fraction (LVEF) must be evaluated to ensure that baseline LVEF is within the institutional limits of normal (see **WARNINGS AND**

SPECIAL PRECAUTIONS). LVEF must continue to be monitored during treatment with lapatinib to ensure that LVEF does not decline below the institutional lower limit of normal (see ***dose delay and dose reduction - cardiac events***).

TYKERB should be taken at least one hour before, or at least one hour after food (see ***Pharmacokinetic properties* - Absorption**). The recommended daily TYKERB dose should not be divided.

Missed doses should not be replaced and the dosing should resume with the next scheduled daily dose (see **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**).

HER2+ over expressing metastatic breast cancer:

TYKERB in combination with capecitabine:

The recommended dose of TYKERB is 1 250 mg (i.e. five tablets) once daily continuously.

The recommended dose of capecitabine is 2 000 mg/m2/day taken in 2 doses 12 hours apart on days 1 - 14 in a 21 day cycle.

Capecitabine should be taken with food or within 30 minutes after food (see ***Pharmacokinetic properties* - Absorption**).

TYKERB in combination with paclitaxel:

The recommended dose of TYKERB is 1 500 mg (i.e. 6 tablets) once daily in combination with paclitaxel. When co-administered with TYKERB, the recommended dose of paclitaxel is 80 mg/m^2 on days 1, 8 and 15 of a 28 day schedule. Alternatively paclitaxel may be given at a dose of 175 mg/m^2 every 21 days.

Hormone-sensitive metastatic breast cancer:

The recommended dose of TYKERB is 1 250 mg (i.e. five tablets) once daily continuously.

When TYKERB is co-administered with the aromatase inhibitor letrozole, the recommended dosage for letrozole is 2,5 mg once daily.

Dose delay and dose reduction (HER2+ over expressing/Hormone- sensitive metastatic breast cancer):

Cardiac events (see WARNINGS AND SPECIAL PRECAUTIONS):

TYKERB should be discontinued in patients with symptoms associated with decreased LVEF that are National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or greater or if their LVEF drops below the institutions lower limit of normal. TYKERB may be restarted at a lower dose (reduced from 1 250 mg/day to 1 000 mg/day or from 1 500 mg/day to 1 250 mg/day after a minimum of 2 weeks and if the LVEF recovers to normal and the patient is asymptomatic. LVEF decreases may occur during the entire span of treatment with TYKERB.

Interstitial lung disease/pneumonitis (see **WARNINGS AND SPECIAL PRECAUTIONS** and **SIDE EFFECTS**): TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are NCI CTCAE grade 3 or greater.

Diarrhoea (see **WARNINGS AND SPECIAL PRECAUTIONS** and **SIDE EFFECTS**)

Lapatinib dosing should be interrupted in patients with diarrhoea which is NCI CTCAE grade 3 or grade 1 or 2 with complicating features (moderate to severe abdominal cramping, nausea or vomiting greater than or equal to NCI CTCAE grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding or dehydration). Lapatinib may be reintroduced at a lower dose (reduced from 1000 mg/day to 750 mg/day, from 1250 mg/day to 1000 mg/day or from 1500 mg/day to 1250 mg/day) when diarrhoea resolves to grade 1 or less. Lapatinib dosing should be permanently discontinued in patients with diarrhoea which is NCI CTCAE grade 4.

Severe Cutaneous Reactions (see **WARNINGS AND SPECIAL PRECAUTIONS**):

Lapatinib should be discontinued in patients who experience severe progressive skin rash with blisters or mucosal lesions.

Other toxicities: Discontinuation or interruption of dosing with TYKERB should be considered when a patient develops toxicity greater than or equal to grade 2 on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Dosing can be restarted at 1 250 mg/day or 1 500 mg/day when administered with an aromatase inhibitor, when the toxicity improves to grade 1 or less. If the toxicity recurs, then TYKERB should be restarted at a lower dose (reduced from 1 250 mg/day to 1 000 mg/day or from 1 500 mg/day to 1 250 mg/day). The prescribing information for capecitabine must be consulted for guidance on dose delay and dose reduction recommendations for capecitabine.

Renal Impairment: There is no experience of TYKERB in patients with severe renal impairment (see ***Pharmacokinetic properties* - Special Patient Populations**).

Hepatic Impairment: Lapatinib is metabolised in the liver. Moderate and severe hepatic impairment have been associated, respectively, with 56 % and 85 % increases in systemic exposure after a single dose of 100 mg (see **CONTRA-INDICATIONS, WARNINGS AND SPECIAL PRECAUTIONS**, and ***Pharmacokinetic properties***).

Administration of TYKERB to patients with mild hepatic impairment should be undertaken with caution due to increased exposure to the medicine (see **WARNINGS AND SPECIAL PRECAUTIONS** and ***Pharmacokinetic properties* – Special Patient Populations**).

Children: The safety and efficacy of TYKERB in paediatric patients has not been established.

Elderly: There are limited data of the use of TYKERB in patients aged 65 years and older. Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N=164) 15 % were 65 and over and 1 % were 75 and over. No overall differences in safety of the combination of TYKERB and capecitabine were observed between these subjects and younger subjects.

Of the total number of hormone-sensitive metastatic breast cancer patients in the clinical studies of lapatinib in combination with letrozole (N=642) 44 % were 65 and over. No overall differences in safety of the combination of lapatinib and letrozole were observed between these subjects and younger subjects.

Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Similarly no differences in effectiveness for the combination of either TYKERB and capecitabine or TYKERB and letrozole on the basis of age were observed.

SIDE EFFECTS:

Safety of TYKERB has been evaluated as monotherapy or in chemotherapies for various cancers in more than 19 000 patients, including 164 patients who received TYKERB in combination with capecitabine, 222 patients who received TYKERB in combination with paclitaxel (80 mg/m^2), 293 patients who received paclitaxel (175 mg/m^2) and 654 patients who received TYKERB in combination with letrozole.

The following convention has been utilised for the classification of frequency: Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 1/1 000) and very rare (< 1/10 000).

Clinical Trial Data:

Metabolism and nutrition disorders:

Very common: anorexia

Cardiac disorders:

Common: decreased left ventricular ejection fraction# †(see **DOSAGE AND DIRECTIONS FOR USE - dose delay and dose reduction - cardiac events** and **Warnings AND SPECIAL PRECAUTIONS).**

#†Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 3 % of patients treated with TYKERB and were asymptomatic in more than 75 % of cases. LVEF decreases resolved or improved in more than 60 % of cases on discontinuation of treatment with TYKERB. Symptomatic LVEF decreases were observed in approximately 0,2 % of patients who received TYKERB. Observed symptoms included dyspnoea, cardiac failure and palpitations.

Respiratory, thoracic and mediastinal disorders:

Uncommon: interstitial lung disease/pneumonitis

Gastrointestinal disorders:

Very common: diarrhoea, which may lead to dehydration (see **DOSAGE AND DIRECTIONS FOR USE - dose delay and dose reduction - other toxicities** and **WARNINGS AND SPECIAL PRECAUTIONS**). Nausea, vomiting

Hepatobiliary disorders:

Uncommon: hyperbilirubinaemia*, hepatotoxicity

* Elevated bilirubin may be due to lapatinib inhibition of hepatic uptake of OATP1B1 or inhibition of excretion into bile by Pgp or BCRP.

Skin and subcutaneous tissue disorders:

Very common: rash (including dermatitis acneform) (see **DOSAGE AND DIRECTIONS FOR USE - dose delay and dose reduction - other toxicities**)

Common: nail disorders including paronychia

Immune system disorders:

Rare: hypersensitivity reactions including anaphylaxis (see **CONTRA-INDICATIONS**)

General disorders and administration site conditions:

Very common: fatigue.

The following additional adverse reactions have been reported to be associated with combination therapy:

Body system category	Very common	Common
1. TYKERB in combination with capecitabine with a frequency difference of greater than 5 % compared to capecitabine alone.		

These data are based on exposure to this combination in 164 patients.		
Gastrointestinal disorders:	dyspepsia	
Skin and subcutaneous tissue disorders:	dry skin	
2. TYKERB in combination with capecitabine but were seen at a similar frequency in the capecitabine alone arm.		
Gastrointestinal disorders:	stomatitis, constipation, abdominal pain	
Skin and subcutaneous tissue disorders:	Palmar-plantar erythrodysaesthesia	
General disorders and administrative site conditions:	Mucosal inflammation	
Muskuloskeletal and connective tissue disorders:	pain in extremity, back pain	
Nervous system disorders:		headache

Psychiatric disorders:	insomnia	
3. TYKERB in combination with paclitaxel (80 mg/m^2) with a frequency difference of greater than 5 % compared to paclitaxel alone. These data are based on exposure to this combination in 222 patients.		
Blood and lymphatic system disorders:	neutropaenia, leucopaenia, anaemia	
Nervous system disorders:	neuropathy, peripheral*	
Muskuloskeletal and connective tissue disorders:	myalgia*	
4. TYKERB in combination with letrozole with a frequency difference of greater than 5 % compared to letrozole alone. These data are based on exposure to this combination in 654 patients.		
Respiratory thoracic and mediastinal disorders:	epistaxis	
Skin and subcutaneous tissue disorders:	alopecia, dry skin	

Post Marketing Data

The following side effects have been derived from post-marketing experience with TYKERB via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, side effects are presented in order of decreasing seriousness.

Cardiac disorders:
Ventricular arrhythmias/Torsades de Pointes (TdP)
Electrocardiogram QT prolonged
Skin and subcutaneous tissue disorders:
Severe cutaneous adverse reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no specific antidote for the inhibition of EGFR (ErbB1) and/or HER2+/neu (ErbB2+) tyrosine phosphorylation.

Symptoms and Signs:

Asymptomatic and symptomatic cases of overdose have been reported in patients being treated with TYKERB. Symptoms observed include known lapatinib associated events (see **SIDE EFFECTS**) and in cases sore scalp, sinus tachycardia (with otherwise normal ECG) and/or mucosal inflammation.

One patient who took an overdose of 3 000 mg of TYKERB for 10 days suffered grade 3 diarrhoea and vomiting on day 10. The symptoms resolved following IV hydration and interruption of treatment with TYKERB and letrozole.

Treatment:

TYKERB is not significantly renally excreted and is highly bound to plasma proteins, therefore haemodialysis would not be expected to be an effective method to enhance the elimination of lapatinib.

Further management should be as clinically indicated or as recommended by the national poison centre, where available.

IDENTIFICATION:

TYKERB Tablets are oval, biconvex, yellow, film-coated tablets, with one side plain and the opposite side debossed with 'GS XJG'.

PRESENTATION:

TYKERB Tablets are supplied in foil-foil (polyamide/aluminium foil/polyvinylchloride (PVC) laminate sealed with aluminium foil lidding) blister strips of 10 tablets, in packs of 70.

Multipacks consist of 2 x 70 tablet packs wrapped together.

Or:

White, round, opaque, high-density polyethylene (HDPE) bottle with a two-piece child-resistant closure (Push & Turn Assembly) in pack size of 70 tablets. The HDPE bottle has an inner heat-seal.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep out of the reach of children.

REGISTRATION NUMBER:

42/26/0275

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City

Jukskei View

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2090

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 01 October 2010

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