NEW ZEALAND DATA SHEET

1 PRODUCT NAME

TYKERB 250 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TYKERB 250 mg film coated tablets contain 405 mg of lapatinib ditosilate monohydrate, equivalent to 250 mg lapatinib free base.

3 PHARMACEUTICAL FORM

Yellow, oval, biconvex, film-coated tablets, with one side plain and the opposite side debossed with GS XJG.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

HER2-positive (HER2+) overexpressing metastatic breast cancer

• TYKERB, in combination with capecitabine, is indicated for the treatment of patients with advanced /metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and whose tumours have progressed after treatment with an anthracycline and a taxane, and who have progressed on prior trastuzumab therapy in the metastatic setting.

• TYKERB, in combination with paclitaxel, is indicated for the first-line treatment of patients with metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom trastuzumab is not appropriate (see Section 5.1 – PHARMACODYNAMIC PROPERTIES, CLINICAL STUDIES).

Hormone receptor-positive metastatic breast cancer

• TYKERB, in combination with an aromatase inhibitor, is indicated for the treatment of post-menopausal women with hormone receptor-positive metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom hormonal therapy is indicated (see Section, 5.1 – PHARMACODYNAMIC PROPERTIES, CLINICAL STUDIES).

4.2 Dose and method of administration

TYKERB treatment should only be initiated by a physician 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 Section 4.4, SPECIAL

WARNINGS AND PRECAUTIONS FOR USE). LVEF must continue to be monitored during treatment with TYKERB 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 Section 4.5, INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION and Section 5.2, 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 Section 4.9, OVERDOSE).

Consult the data sheet of the co-administered medicinal product should be consulted for details of its dosage, contraindications, and safety information.

HER2-positive overexpressing metastatic breast cancer

General target population

TYKERB in combination with capecitabine

The recommended dose of TYKERB is 1250 mg (i.e. 5 tablets) once daily continuously when taken in combination with capecitabine.

The recommended dose of capecitabine is 2000 mg/m^2/day taken in 2 doses, 12 hours apart, on days 1-14 in a 21-day cycle (see Section 5.1 – PHARMACODYNAMIC PROPERTIES, CLINICAL STUDIES). Capecitabine should be taken with food or within 30 minutes after food.

TYKERB in combination with paclitaxel

The recommended dose of TYKERB is 1500 mg (i.e. 6 tablets) once daily continuously in combination with paclitaxel. 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 (see 5.1 – PHARMACODYNAMIC PROPERTIES, CLINICAL STUDIES).

TYKERB in combination with an aromatase inhibitor

The recommended dose of TYKERB is 1500 mg (i.e. 6 tablets) once daily continuously when taken in combination with an aromatase inhibitor.

When TYKERB is co-administered with the aromatase inhibitor letrozole, the recommended dose of letrozole is 2.5 mg once daily. If TYKERB is co-administered with an alternative aromatase inhibitor, please refer to the data sheet of the medicinal product for dosing details.

Special populations

Renal impairment

There is no experience of TYKERB in patients with severe renal impairment. However, patients with renal impairment are unlikely to require dose modification of TYKERB given that under 2% of an administered dose (lapatinib and metabolites) is eliminated renally (see Section 5.2, PHARMACOKINETIC PROPERTIES - Special populations: Patients with renal impairment).

Hepatic Impairment

Lapatinib (TYKERB) is metabolized in the liver. Moderate and severe hepatic impairment have been associated with increases in systemic exposure. TYKERB administration to patients with hepatic impairment requires caution due to increased exposure.

Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1250 mg/day to 750 mg/day or from 1500 mg/day to 1000 mg/day in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range. However, there are no clinical data with this dose adjustment in patients with severe hepatic impairment (see Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2, P HARMACOKINETIC PROPERTIES – Patients with hepatic Impairment).

Paediatric patients (below 18 years)

The safety and efficacy of TYKERB in patients below 18 years of age has not been established.

Geriatric patients (65 years or above)

There are limited data on the use of TYKERB in patients aged 65 years and older (see Table 1). No overall differences in the safety or efficacy of these regimens based on age were observed. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Greater sensitivity of elderly individuals cannot be ruled out.

Table 1 Exposure in Elderly Patients

	Patient age (years)	
	≥ 65	≥ 75
TYKERB + capecitabine (N=198) (EGF100151)	33 (17%)	2 (1%)
TYKERB + paclitaxel (N=222) (EGF 104535)	16 (7%)	0
TYKERB + letrozole (N=642) (EGF30008)	285 (44%)	77 (12%)
Single agent TYKERB (N=599) (EGF20002, EGF20008, EGF20009, EGF103009)	101 (17%)	24 (4%)

Dose delay and dose reduction (all indications)

Cardiac events

TYKERB should be interrupted 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 (LLN). TYKERB may be restarted at a lower dose (1000 mg/day when administered with capecitabine and 1250 mg/day when administered with an aromatase inhibitor) after a minimum of 2 weeks

and if the LVEF recovers to normal and the patient is asymptomatic. Based on current data, the majority of LVEF decreases occur within the first 12 weeks of treatment, however, there is limited data on long term exposure. See Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Interstitial lung disease/pneumonitis

TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are NCI CTCAE grade 3 or higher. See Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8, UNDESIRABLE EFFECTS.

Diarrhoea

TYKERB 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). TYKERB 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. TYKERB should be permanently discontinued in patients with NCI CTCAE grade 4 diarrhoea. See Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8, UNDESIRABLE EFFECTS.

Severe Cutaneous Reactions

TYKERB should be discontinued in patients who experience severe progressive skin rash with blisters or mucosal lesions. See Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE .

Other toxicities

Discontinuation or interruption of TYKERB may be considered if a patient develops toxicity greater than or equal to NCI CTCAE grade 2. Dosing can be restarted at the standard dose of 1250 mg/day or 1500 mg/day, when the toxicity improves to grade 1 or less. If the toxicity recurs, then TKERB should be restarted at a lower dose (reduced from 1250 mg/day to 1000 mg/day or from 1500 mg/day to 1250 mg/day).

Dose delay and dose reduction (administration with paclitaxel)

Discontinuation or interruption of dosing with TYKERB may be considered when a patient develops toxicity greater than or equal to grade 2 on the NCI CTCAE. Dosing can be restarted at 1500 mg/day when toxicity improves to grade 1 or less. If the toxicity recurs, then TYKERB should be restarted at 1250 mg/kg.

Taxanes are also associated with bone marrow suppression and other toxicities. The full data sheet for paclitaxel should be referred to for advice on dose delay and dose reduction of paclitaxel.

4.3 Contraindications

TYKERB is contraindicated in patients with hypersensitivity to any of the ingredients (see Section 6,1 – LIST OF EXCIPIENTS and Section 4.8 UNDESIRABLE EFFECTS).

4.4 Special warnings and precautions for use

Cardiac toxicity

Left ventricular ejection fraction [LVEF]

TYKERB has been associated with reports of decreases in LVEF (see Section 4.8, UNDESIRABLE 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 TYKERB 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 TYKERB to ensure that LVEF does not decline to an unacceptable level (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - dose delay and dose reduction - cardiac events and Section 5.1, PHARMACODYNAMIC PROPERTIES, CLINICAL STUDIES).

In studies across the TYKERB clinical development program, cardiac events, including LVEF decreases were reported in approx. 1 % of patients. Symptomatic LVEF decreases were observed in approx. 0.3 % of patients who received TYKERB. However, if TYKERB was administered in combination with trastuzumab in the metastatic setting, the incidence of cardiac events including LVEF decreases was higher (7 %) versus the TYKERB monotherapy arm (2 %). The cardiac events observed in this study were comparable in nature and severity to those previously seen with TYKERB.

QT prolongation

A concentration dependent increase in QTc interval has been observed in a dedicated placebo-controlled, crossover study of TYKERB in patients with advanced solid tumours.

Study EGF114271

The effect of lapatinib on the QTc-interval was evaluated in a single-blind, placebo-controlled, single sequence (placebo and active treatment) crossover study in patients with advanced solid tumours (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 PD 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 PK/PD analyses

confirmed the presence of a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.

Caution should be taken if TYKERB is administered to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalaemia or hypomagnesemia, congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation. Hypokalaemia, hypocalcaemia or hypomagnesemia should be corrected prior to TYKERB administration.

Interstitial lung disease and pneumonitis

TYKERB has been associated with reports of interstitial lung disease and pneumonitis (see Section 4.8, UNDESIRABLE EFFECTS). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION).

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 (<1% of patients) and post marketing experience. The hepatotoxicity may be severe and deaths have been reported, although the relationship to TYKERB is uncertain. The hepatotoxicity may occur days to several months after initiation of treatment.

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 Section 4.8, UNDESIRABLE EFFECTS).

Patients who carry the HLA alleles DQA1*02:01 and DRB1*07:01 have increased risk of TYKERB-associated hepatotoxicity. In a large, randomised clinical trial of TYKERB monotherapy (n=1,194), the overall risk of severe liver injury (ALT > 5 times the upper limit of normal, NCI CTCAE grade 3) was 2% (1:50), the risk in DQA1*02:01 and DRB1*07:01 allele carriers was 8% (1:12) and the risk in non-carriers was 0.5% (1:200). Carriage of the HLA risk alleles is common (15 to 25%) in Caucasian, Asian, African and Hispanic populations but lower (1%) in Japanese populations.

If TYKERB is to be administered to patients with severe pre-existing hepatic impairment, dose reduction is recommended. In patients who develop severe hepatotoxicity while on therapy, TYKERB should be discontinued permanently (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION and Section 5.2, PHARMACOKINETIC PROPERTIES - Special patient Populations).

Diarrhoea

Diarrhoea, including severe diarrhoea, has been reported with lapatinib treatment (see Section 4.8, UNDESIRABLE EFFECTS). Diarrhoea may be severe, and deaths have been reported. Diarrhoea generally occurs early during TYKERB treatment, with almost half of

those patients with diarrhoea first experiencing it within 6 days. This usually lasts 4-5 days. TYKERB-induced diarrhoea is usually low-grade, with severe diarrhoea of NCI CTCAE grades 3 and 4 occurring in < 10 % and < 1 % of patients, respectively. 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 such as loperamide after the first unformed stool is recommended. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, use of antibiotics such as fluoroquinolones (especially if diarrhoea is persistent beyond 24 hours, there is fever, or grade 3 or 4 neutropenia) and interruption or discontinuation of TYKERB therapy (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION - dose delay and dose reduction - diarrhoea).

Neutropenia

Neutropenia has been reported with TYKERB administered in combination with paclitaxel (see Section 4.8, UNDESIRABLE EFFECTS). Complete blood counts should be monitored regularly during treatment with this combination (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION - Dose Delay and dose reduction - administration with paclitaxel).

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 Section 4.2, DOSE AND METHOD OF ADMINISTRATION).

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 Section 4.5, INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

Limited data suggest that TYKERB in combination with paclitaxel is less effective and not as tolerable as trastuzumab in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer whose tumours overexpress HER2 (ErbB2). Therefore lapatinib-paclitaxel should be used in patients for whom trastuzumab is not appropriate (see Section 5.1, PHARMACODYNAMIC PROPERTIES, CLINICAL STUDIES).

4.5 Interaction with other medicines and other forms of interaction

TYKERB is predominantly metabolised by CYP3A (see Section 5.2, PHARMACOKINETIC PROPERTIES). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of TYKERB.

Interactions with CYP3A4-inhibitors

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.

Coadministration of TYKERB with known inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole or grapefruit juice) should proceed with caution and clinical response and adverse events should be carefully monitored (see Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of TYKERB is predicted to adjust the TYKERB 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 1 week should be allowed before the TYKERB dose is increased to the indicated dose.

Interactions with CYP3A4-inducers

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%.

Co-administration of TYKERB with known inducers of CYP3A4 (e.g., rifampin, rifabutin, carbamazepine, phenytoin or hypericum perforatum (St. John's wort)) requires caution; clinical response and adverse events should be carefully monitored (see Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of TYKERB should be titrated gradually from 1,250 mg/day up to 4,500 mg/day or from 1,500 mg/day up to 5,500 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.

Drugs that affect gastric pH

Pre-treatment with a proton pump inhibitor (esomeprazole) decreased TYKERB exposure by an average of 27% (range: 6% to 49 %). This effect decreases with increasing age from approximately 40 to 60 years. Therefore, caution should be used when TYKERB is used in patients pre-treated with a proton pump inhibitor.

Effect of TYKERB on other drugs

Lapatinib inhibits CYP3A4 *in vitro* at clinically relevant concentrations. Coadministration of TYKERB with orally administered midazolam resulted in an approximate 45 % increase in the AUC of midazolam. There was no clinically meaningful increase in AUC when midazolam was dosed intravenously. Caution should be exercised when dosing TYKERB concurrently with orally administered medications with narrow therapeutic windows that are substrates of CYP3A4 (see Section 5.2, 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 that are substrates of CYP2C8 such as repaglinide (see Section 5.2, PHARMACOKINETIC PROPERTIES).

Combination therapy and non-fixed dose combination therapy

Coadministration 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 when TYKERB is coadministered with paclitaxel.

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

Coadministration 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 coadministered with irinotecan.

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

Effect of TYKERB on transport proteins

Lapatinib is a substrate for the transport proteins Pgp and BCRP (Breast Cancer Resistance Protein). Inhibitors and inducers of these proteins may alter the exposure and/or distribution of lapatinib (see Section 5.2, PHARMACOKINETIC PROPERIES).

Lapatinib inhibits the transport protein Pgp *in vitro* at clinically relevant concentrations. Coadministration of TYKERB with orally administered digoxin resulted in an approximate 98% increase in the AUC of digoxin. Caution should be exercised when dosing TYKERB concurrently with medications with narrow therapeutic windows that are substrates of Pgp (e.g. quinidine).

Lapatinib inhibits the transport proteins BCRP and OATP1B1 *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, quinidine) and OATP1B1 (e.g. rosuvastatin) (see Section 5.2, PHARMACOKINETIC PROPERTIES)

Drug-food/drink interactions

The bioavailability of TYKERB is affected by food (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION and Section 5.2, PHARMACOKINETIC PROPERTIES).

Grapefruit juice may inhibit CYP3A4 and Pgp in the gut wall, thereby it may increase the bioavailability of lapatinib and should therefore be avoided during treatment with TYKERB (see Section 5.2, PHARMACOKINETIC PROPERTIES).

4.6 Fertility, pregnancy and lactation

Infertility

The effect of lapatinib on human fertility is unknown. See Section 5.3, PRECLINICAL SAFETY DATA.

Use in Pregnancy

There are no adequate and well-controlled studies of TYKERB in pregnant women to assess the risks. The effect of TYKERB on human pregnancy is unknown. Pregnant women should be advised of the potential risk to the foetus and TYKERB should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with TYKERB.

TYKERB was not teratogenic when studied in pregnant rats and rabbits but caused minor abnormalities at doses which were maternally toxic (see Section 5.3, PRECLINICAL SAFETY DATA).

Contraception

Based on findings in animal studies, lapatinib can cause foetal harm. Females of reproductive potential must be advised to use effective contraception (methods that result in less than 1 % pregnancy rates) and avoid becoming pregnant while receiving treatment with TYKERB and for at least 5 days after the last dose. If the drug is used during pregnancy or if the patient becomes pregnant while receiving the drug, the patient should be notified that TYKERB may cause harmful effects to the human foetus or neonate.

Use in Lactation

There are no data on the presence of lapatinib in human milk, or the effect of lapatinib on the breastfed infant, or on milk production. As many drugs are transferred into human milk and due to the potential for serious adverse drug reactions in breast-fed infants from lapatinib, it is advised that that women should not breast-feed while receiving therapy with TYKERB and for at least 5 days after the last dose.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of TYKERB on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of the TYKERB. 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.

4.8 Undesirable effects

Summary of the safety profile

Clinical trial data

The safety of TYKERB has been evaluated as monotherapy and in combination with other chemotherapies for various cancers in more than 19,000 patients, including 198 patients who received lapatinib in combination with capecitabine, 222 patients who received TYKERB in combination with paclitaxel (80 mg/m^2 weekly), 293 patients who received TYKERB in combination with paclitaxel (175 mg/m^2 every 3 weeks), and 654 patients who received TYKERB in combination with letrozole (see Section 5.1, PHARMACODYNAMIC PROPERTIES, CLINICAL STUDIES).

Tabulated summary of adverse drug reactions (ADRs) from clinical trials

Adverse effects from clinical trials are listed by MedDRA system organ class (SOC) in the tables 2 to 6. The following convention has been utilised for the classification of frequency in all of the AE tables:

Very common:	Greater than or equal to 1/10
Common:	Greater than or equal to 1/100 and less than 1/10
Uncommon:	Greater than or equal to 1/1000 and less than 1/100
Rare:	Greater than or equal to 1/10,000 and less than 1/1000
Very rare:	Less than 1/10,000.

TYKERB monotherapy

The following adverse reactions (Table 2) have been reported to be associated with TYKERB monotherapy.

Table 2 Adverse reactions occurring with TYKERB monotherapy

Immune system disorders	
Rare	Hypersensitivity reactions including anaphylaxis[1]
Metabolism and nutrition disorders	
Very common	Anorexia
Cardiac disorders	
Common	Decreased left ventricular ejection fraction[2]
Respiratory, thoracic and mediastinal disorders	
Uncommon	Interstitial lung disease / pneumonitis[3]
Gastrointestinal disorders	
Very common	Diarrhoea, which may lead to dehydration[4], nausea, vomiting

Hepatobiliary disorders	
Very common	Hyperbilirubinaemia[5]
Uncommon	Hepatotoxicity[6]
Skin and subcutaneous tissue disorders	
Very common	Rash[4] (including dermatitis acneform)
Common	Nail disorders including paronychia
General disorders and administration site conditions	
Very common	Fatigue

[1] See Section 4.3, CONTRAINDICATIONS.

[2] Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 1% of patients and were asymptomatic in more than 70% of cases. LVEF decreases resolved or improved in more than 70% of cases on discontinuation of treatment with lapatinib. Symptomatic LVEF decreases were observed in approximately 0.3 % of patients who received lapatinib. Observed symptoms included dyspnoea, cardiac failure and palpitations. See Section 4.2, DOSE AND METHOD OF ADMINISTRATION - dose delay and dose reduction - Cardiac events and Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

[3] See Section 4.2, DOSE AND METHOD OF ADMINISTRATION and Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

[4] Diarrhoea and rash were generally low grade (most events of diarrhoea were grade 1 or 2) and did not result in discontinuation of treatment with TYKERB. Diarrhoea responds well to proactive management (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION - Dose delay and dose reduction: Diarrhoea). Rash was transient in the majority of cases. See Section 4.2, DOSE AND METHOD OF ADMINISTRATION - Dose delay and dose reduction (all indications) – Other toxicities.

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

6 ALT or AST >3 times ULN and total bilirubin >1.5 times ULN or serious hepatobiliary events associated with lapatinib or Hy's law cases.

<u>TYKERB in combination with capecitabine</u>

Study EGF100151

In addition to the adverse reactions observed with TYKERB monotherapy, the following adverse reactions have been reported to be associated with TYKERB in combination with capecitabine in study EGF100151 with a frequency difference of greater than 5% compared to capecitabine alone (Table 3.). These data are based on exposure to this combination in 198 patients.

Table 3 Adverse reactions reported to be associated with TYKERB in combination with capecitabine at a frequency difference of > 5% compared to capecitabine alone

Gastrointestinal disorders	
Very common	Dyspepsia

Skin and subcutaneous tissue disorders	
Very common	Dry skin

The following adverse reactions (Table 4) were reported to be associated with TYKERB in combination with capecitabine but were seen at a similar frequency in the capecitabine alone arm.

Table 4 Additional ADRs occurring in EGF100151 with a similar frequency for the combination versus capecitabine alone

Gastrointestinal disorders	
Very common	Stomatitis, constipation, abdominal pain
Skin and subcutaneous tissue disorders	
Very common	Palmar-plantar erythrodysaesthesia
General disorders and administrative site conditions	
Very common	Mucosal inflammation.
Musculoskeletal and connective tissue disorders	
Very common	Pain in extremity, back pain
Nervous system disorders	
Common	Headache
Psychiatric disorders	
Very common	Insomnia

A subsequent post-hoc analysis inclusive of 75 subjects who were enrolled into the study between the interim analysis clinical cut-off date and halting enrollment into the study (n=198 combination arm vs n= 191 control arm) was performed. No difference in the safety profile was observed from that described previously.

In this analysis, 4% (7 subjects) treated with the combination arm and 1% (2 subjects) in the control arm experienced a decreased LVEF, although none were fatal and did not result in permanent discontinuation from the study.

TYKERB in combination with paclitaxel

Study EGF104535

In addition to the adverse reactions observed with TYKERB monotherapy, the following adverse reactions (Table 5) have been reported to be associated with TYKERB in combination with paclitaxel (80 mg/m^2 weekly) with a frequency difference of greater than 5 % compared to paclitaxel alone. These data are based on exposure to this combination in 222 patients in study EGF104535.

Table 5 Additional ADRs occurring in EGF104535 with a frequency difference of > 5 % compared to paclitaxel

Blood and lymphatic system disorders	
Very common	Neutropenia, Leukopenia, Anaemia
Nervous system disorders	
Very common	Neuropathy peripheral. *
Musculoskeletal and connective tissue disorders	
Very common	Myalgia. *
* Additional adverse reactions reported in 293 patients on lapatinib in combination with paclitaxel (175 mg/m^2 every 3 weeks) with a frequency difference of greater than 5% compared to paclitaxel alone.	

TYKERB in combination with Letrozole

Study EGF30008

In addition to the adverse reactions observed with TYKERB monotherapy, the following additional adverse reactions (Table 6) have been reported to be associated with TYKERB in combination with letrozole in study EGF30008 with a frequency difference of greater than 5% compared to letrozole alone. These data are based on exposure to this combination in 654 patients.

Table 6 ADRs occurring with a frequency difference of > 5 % versus letrozole alone in study EGF30008

Respiratory, thoracic and mediastinal disorders	
Very Common	Epistaxis
Skin and subcutaneous tissue disorders	
Very Common	Alopecia, Dry skin

Post Marketing Data

The following adverse drug reactions 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, ADRs are presented in order of decreasing seriousness (Table 7).

Table 7 ADRs from spontaneous reports and literature

Cardiac disorders	
Unknown	Ventricular arrhythmias/Torsades de Pointes (TdP), Electrocardiogram QT prolonged
Skin and subcutaneous tissue disorders	
Unknown	Severe cutaneous adverse reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
Common	Skin fissures[1]

[1] Frequency of skin fissures in pooled clinical trials data set was 4.9% (common)

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

There is no specific antidote for the inhibition of ErbB1 (EGFR) and/or HER2/neu (ErbB2) tyrosine phosphorylation. The maximum oral dose of TYKERB that has been administered in clinical trials is 1800 mg once daily.

More frequent ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical trials, therefore missed doses should not be replaced, and dosing should resume with the next scheduled daily dose (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION).

Symptoms and signs

Asymptomatic and symptomatic cases of overdose have been reported in patients being treated with TYKERB. Symptoms observed include known TYKERB associated events (see Section 4.8, UNDESIRABLE EFFECTS) and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG) and/or mucosal inflammation.

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 Poisons Centre (telephone 0800 POISON or 0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: human epidermal growth factor receptor 2 (HER)2 tyrosine kinase inhibitor, ATC code: L01EH01.

Pharmacodynamic properties

Mechanism of action

Lapatinib is a novel 4-anilinoquinazoline kinase inhibitor with a unique mechanism of action.

Lapatinib is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 (EGFR) and HER2 receptors (estimated Kiapp values of 3nM and 13nM, respectively) with a slow off-rate from these receptors (half-life greater than or equal to 300 minutes). This dissociation rate was found to be slower than other 4-anilinoquinazoline kinase inhibitors studied. Lapatinib inhibits ErbB-driven tumour cell growth *in vitro* and in various animal models.

In addition to its activity as a single agent, an additive effect was demonstrated in an *in vitro* study when lapatinib and 5-FU (the active metabolite of capecitabine) were used in combination in the four tumour cell lines tested. The clinical significance of these *in vitro* data is unknown.

The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against breast cancer cell lines selected for long-term growth in trastuzumab-containing medium *in vitro*. These findings suggest non-cross-resistance between these two HER2 directed agents.

Hormone receptor-positive breast cancer cells (oestrogen receptor [ER] positive and / or progesterone receptor [PgR] positive) that co-express HER2 tend to be resistant to established endocrine therapies. Hormone receptor-positive breast cancer cells that initially lack overexpression of EGFR or HER2 will up regulate these receptors as the tumour becomes resistant to endocrine therapy. Randomized trials in hormone receptor-positive metastatic breast cancer indicate that a HER2 or EGFR tyrosine kinase inhibitor may improve PFS when added to endocrine therapy.

Clinical Studies

Data in two randomised trials in metastatic setting have shown that TYKERB combined with chemotherapy is less effective than when combined based treatment regimens. See below for details.

Lapatinib is not indicated in the adjuvant setting.

Combination treatment with TYKERB and capecitabine

Study EGF100151

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was evaluated in a randomised, phase III trial (EGF100151). Patients eligible for enrolment had HER2 over-expressing (ICH 3+ or ICH 2+ and FISH positive), locally advanced or metastatic breast cancer, after prior treatment that included taxanes, anthracyclines and trastuzumab. LVEF was evaluated in all patients (using echocardiogram or MUGA scans) prior to initiation of treatment with TYKERB to ensure baseline LVEF was within the institution's normal limits. In clinical trials, LVEF was monitored at approximately 8–week intervals during treatment with TYKERB to ensure it did not decline to below the institutions lower limit of normal. The majority of LVEF decreases (greater than 60%) were observed during the first nine weeks of treatment, however limited data was available for long term exposure.

Patients were randomized to receive either TYKERB 1250 mg once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or to receive capecitabine alone (2500 mg/m^2/day on days 1-14 every 21 days). Study treatment was given until disease progression, or withdrawal for another reason. The primary endpoint was time to progression (TTP) as assessed by an independent review panel. Results presented below are based on both the investigators assessment and review by an independent review panel.

The results at the data cut-off date of 03 April 2006 (the date at which further enrolment to the study was halted), showed a significant increase in TTP for patients receiving TYKERB plus capecitabine (representing a 43% reduction in the risk of disease progression or death due to breast cancer compared with capecitabine monotherapy, as assessed by the independent review panel). See Table 8.

Table 8 Key efficacy data (TTP, ORR) from Study EGF100151 (TYKERB / capecitabine)

	Independent Assessment		***Investigator Assessment***	
Efficacy Outcome	TYKERB plus capecitabine (N=*198*)	Capecitabine alone (N=201)	TYKERB plus capecitabine (N=198)	Capecitabine alone (N=201)
Time to progression (TPP)				
Progressed or died due to breast cancer	41%	51%	61%	63%
Median time to progression (weeks)	27.1	18.6	23.9	18.3

	Independent Assessment		***Investigator Assessment***	
Efficacy Outcome	TYKERB plus capecitabine (N=*198*)	Capecitabine alone (N=201)	TYKERB plus capecitabine (N=198)	Capecitabine alone (N=201)
Hazard ratio, 95% CI	0.57 (0.43, 0.77)		0.72 (0.56, 0.92)	
(p value)	0.00013		0.00762	
Overall Response Rate				
ORR	23.7%	13.9%	31.8%	17.4%
95% CI	(18.0, 30.3)	(9.5, 19.5)	(25.4, 38.8)	(12.4, 23.4)

CI = confidence interval

The overall response rate, as assessed by an independent review panel was 23.7% for patients receiving TYKERB plus capecitabine and 13.9% for patients receiving capecitabine. Median duration of response was 32.1 weeks and 30.6 weeks respectively.

On the combination arm, there were 4 (2%) progressions in the central nervous system as compared with the 13 (6%) progressions on the capecitabine alone arm, as assessed by an independent review panel.

At the time enrolment was halted to EGF100151 (03 April 2006), 399 patients were randomised to study therapy and 9 other patients were being screened. All 9 patients in screening, and all those already receiving capecitabine monotherapy, were offered combination treatment. In total, 207 patients were assigned to the combination therapy and 201 patients were assigned to capecitabine monotherapy.

An analysis of survival data to 01 October 2008 is summarised in Table 9.

Table 9 Overall Survival (OS) data from Study EGF100151 (TYKERB/ capecitabine)

	TYKERB plus capecitabine (N=207)	Capecitabine alone (N=201)
Overall Survival		
Died	81%	86%
Median overall survival (weeks)	75.0	64.7
Hazard ratio, 95% CI	0.87 (0.71, 1.08)	
(p value)	0.210	

CI = confidence interval

After the study was halted, 36 patients crossed over from capecitabine to TYKERB + capecitabine, of whom 26 crossed over prior to disease progression while on capecitabine alone. To isolate the treatment effect in the presence of cross-over, Cox regression analysis

considering crossover as a time-dependent covariate and treatment effect was performed. The results from this analysis suggest a clinically relevant reduction in risk of death by 20%, with a treatment effect hazard ratio of 0.80 (95% confidence interval [CI]: 0.64, 0.99; p=0.043).

Study EGF111438

A randomised Phase III study (EGF111438) (N=540) compared the effect of TYKERB in combination with capecitabine relative to trastuzumab in combination with capecitabine on the incidence of CNS as site of first relapse in women with HER2 overexpressing metastatic breast cancer. Patients were randomised to either TYKERB 1250 mg once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or trastuzumab (loading dose of 8 mg/kg followed by 6 mg/kg infusions every 3 weeks) plus capecitabine (2500 mg/m^2/day, days 1-14, every 21 days). Randomisation was stratified by prior trastuzumab treatment and number of prior treatments for metastatic disease (none versus ≥ 1 line). The study was stopped when a pre-planned interim analysis (N=475) showed superior efficacy of the trastuzumab plus capecitabine arm and a low incidence of CNS events.

The final analysis confirmed that the results of the primary endpoint were inconclusive due to a low number of CNS events [8 patients (3.2%) in the TYKERB plus capecitabine arm experienced CNS metastasis as site of first progression, compared with 12 patients (4.8%) in the trastuzumab plus capecitabine arm]. The final results of progression free survival and overall survival are shown in Table 10. The final analysis confirmed the superior efficacy of trastuzumab plus capecitabine arm.

Table 10 Analyses of Investigator-Assessed Progression-Free Survival (PFS) and Overall Survival (OS) in Study EGF111438

	Investigator-Assessed PFS		**Overall Survival**	
	TYKERB + capecitabine	Trastuzumab + capecitabine	TYKERB + capecitabine	Trastuzumab + capecitabine
All patients				
N	271	269	271	269
Number (%) with Event[1]	59%	50%	26%	22%
Kaplan-Meier estimate, months [a]				
Median (95% CI)	6.6 (5.7, 8.1)	8.0 (6.1, 8.9)	22.7 (19.5, -)	27.3 (23.7, -)
Stratified Hazard ratio [b]				
HR (95% CI)	1.30 (1.04, 1.64)		1.34 (0.95, 1.90)	
p-value	0.021		0.095	
Patients who had received prior trastuzumab				

	Investigator-Assessed PFS		Overall Survival	
	TYKERB + capecitabine	Trastuzumab + capecitabine	TYKERB + capecitabine	Trastuzumab + capecitabine
N	167	159	167	159
Number (%) with Event[1]	103 (62)	86 (54)	43 (26)	38 (24)
Median (95% CI)	6.6 (5.7, 8.3)	6.1 (5.7, 8.0)	22.7 (20.1,-)	27.3 (22.5, 33.6)
HR (95% CI)	1.13 (0.85, 1.50)		1.18 (0.76, 1.83)	
Patients who had not received prior trastuzumab				
N	104	110	104	110
Number (%) with Event[1]	57 (55)	48 (44)	27 (26)	20 (18)
Median (95% CI)	6.3 (5.6, 8.1)	10.9 (8.3, 15.0)	NE[2] (14.6, -)	NE[2] (21.6, -)
HR (95% CI)	1.70 (1.15, 2.50)		1.67 (0.94, 2.96)	

CI = confidence interval

a. PFS was defined as the time from randomisation to the earliest date of disease progression or death from any cause, or to the date of censor.

b. Pike estimate of the treatment hazard ratio, >1 indicates a higher risk for TYKERB plus capecitabine compared with Trastuzumab plus capecitabine.

1. PFS event is Progressed or Died and OS event is Died due to any cause.

2. NE=Median was not reached.

Combination treatment with TYKERB and paclitaxel

Study EGF104535

The efficacy and safety of TYKERB in combination with paclitaxel in breast cancer were evaluated in a randomised phase III trial, EGF104535. Patients had histologically confirmed invasive breast cancer (Stage IV disease) that overexpress HER2 and had not received prior therapy for metastatic disease.

Patients were randomly assigned to paclitaxel (80 mg/m^2 intravenous on days 1, 8, and 15 of a 28-day schedule) and either TYKERB 1500 mg/day or placebo once daily. Patients received a minimum of 6 cycles of TYKERB or placebo plus paclitaxel. After the 6 cycles of combination with paclitaxel were completed, patients continued TYKERB or placebo until disease progression or an unacceptable toxicity occurred. The primary endpoint was overall survival (OS). Four hundred forty-four (444) patients were enrolled in this study. Of the 222 patients who were on paclitaxel plus placebo, 149 patients (67%) with disease progression entered the open-label extension phase of the study and received TYKERB monotherapy. The median age was 50 years and 7% were older than 65 years. Eighty-six percent (86%) were Asian, 8% Hispanic, and 5% Caucasian. The overall survival data are summarised in Table 11 and

represented graphically in Figure 1. A summary of other efficacy endpoints are provided in Table 12.

Figure 1 **Kaplan-Meier Estimates of Overall Survival (ITT Population) for combination treatment with TYKERB and paclitaxel (80 mg/m^2) in study EGF104535**

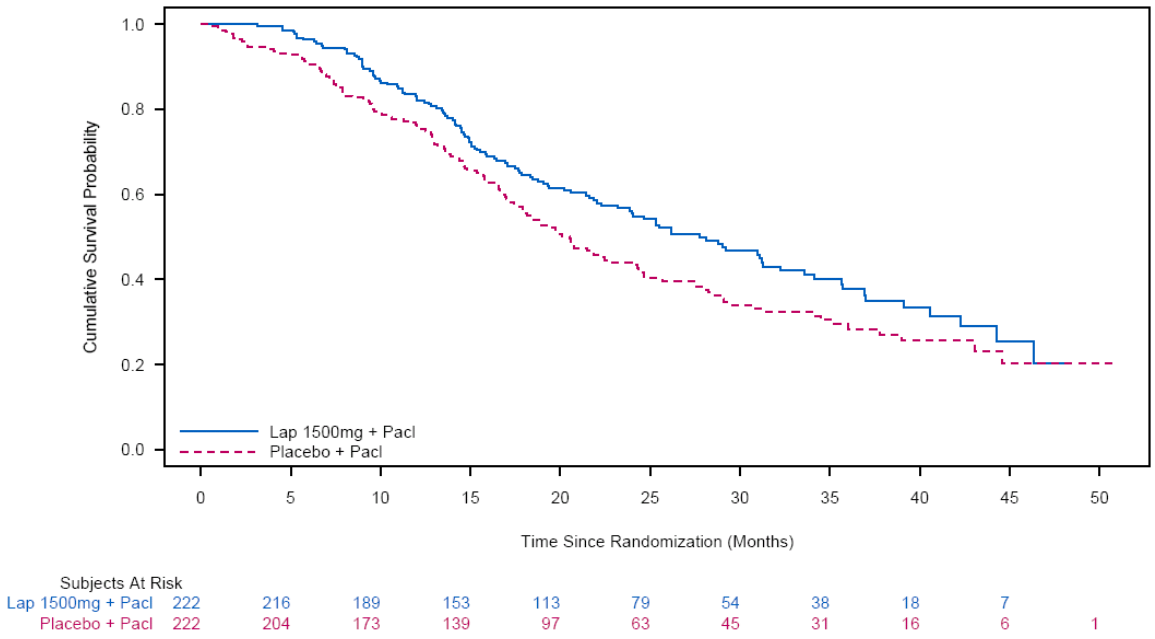


Table 11 **Overall Survival Data for Combination treatment with TYKERB and paclitaxel (80 mg/m^2) in study EGF104535**

Efficacy outcome	**TYKERB plus Paclitaxel (N = 222)**	**Paclitaxel plus placebo (N = 222)**
Died	54%	64%
Median overall survival (months)[1] (95% CI)	27.8 (23.2, 32.2)	20.5 (17.9, 24.3)
Hazard ratio[2], 95% CI (Two-sided P value)	0.74 (0.58, 0.94) 0.0124	
Cox Regression[3] Hazard Ratio 95% CI (Two-sided P value)	0.64 (0.49, 0.82) 0.0005	

CI = confidence interval

[1] Kaplan-Meier estimates

[2] Pike estimator of hazard ratio

[3] Adjusted for hormonal status, metastatic disease sites, stage at initial diagnosis, ECOG Performance Status, number of metastatic sites, age and disease-free interval.

Table 12 Efficacy Data for combination treatment with TYKERB and Paclitaxel (80 mg/m^2) in study EGF104535

	TYKERB plus Paclitaxel (N = 222)	Paclitaxel plus placebo (N = 222)
Median PFS[1], months	9.7	6.5
(95% CI)	(9.2, 11.1)	(5.5, 7.3)
Hazard Ratio (95% CI)	0.52 (0.42, 0.64)	
P value	<0.0001	
Response Rate (%)	69	50
(95% CI)	(62.9, 75.4)	(42.8, 56.3)
Duration of Response, months	9.3	5.8
(95% CI)	(7.7, 10.7)	(5.6, 7.4)

PFS = progression-free survival; CI = confidence interval; [1]Kaplan-Meier estimate.

Study EGF30001

Another randomised, double-blind, controlled study evaluated TYKERB and paclitaxel as first-line therapy for metastatic breast cancer in patients with negative or untested HER2 status and previously untreated in the metastatic setting. Patients (N= 579) were randomly assigned 1:1 to paclitaxel (175 mg/m^2 intravenously over 3 hours on day 1, every 3 weeks) and either TYKERB 1500 mg/day or placebo once daily. Sixty-four percent (64%) were Caucasian, 18% Hispanic, and 11% Asian. There were 91 patients (16%) with HER2 positive disease.

The primary endpoint was time-to-progression (TTP); secondary endpoints included progression free survival (PFS), tumour response rate (RR), clinical benefit rate (CBR), overall survival (OS) and safety. No significant differences in TTP or PFS were observed between treatment arms in unselected ITT population. In the HER2 positive subgroup, statistically significant and clinically relevant benefit was observed in TTP and PFS in favour of the TYKERB plus paclitaxel group. The median TTP in the HER2 positive subgroup was 35.1 weeks in the TYKERB plus paclitaxel group compared to 23.1 weeks in the paclitaxel plus placebo group (hazard ratio of 0.57; 95% CI: 0.34, 0.93; p = 0.011). The median PFS in HER2 positive subgroup was 34.4 weeks (95% CI: 32.1, 41.6) in the TYKERB plus paclitaxel combination compared to 22.6 weeks (95% CI: 20.1, 32.9) in the paclitaxel plus placebo group (hazard ratio of 0.56; 95% CI: 0.34, 0.90; p = 0.007). The overall survival analysis of the ITT population and HER2 positive subgroup are presented in Table 13.

Table 13 Overall Survival data (TYKERB plus paclitaxel 175 mg/m^2) in study EGF30001

	TYKERB plus paclitaxel	Paclitaxel alone
Overall Survival HER2+ Population	**(N=52)**	**(N=39)**
Died	71%	74%
Median overall survival (months) (95% CI)	24.3 (17.7, 31.3)	19.2 (11.7, 29.7)
Hazard ratio, 95% CI (p value)	0.77 (0.5, 1.3) 0.281	

CI = confidence interval

EGF108919

A randomized Phase III study (EGF108919) (N=652) compared the efficacy and safety of TYKERB plus taxane followed by TYKERB alone versus trastuzumab plus taxane followed by trastuzumab alone as first line therapy for women with HER2 positive metastatic breast cancer. Patients were randomized to either TYKERB 1250 mg once daily plus Paclitaxel: 80 mg/m^2 once weekly (Days 1, 8 and 15 of a 4-week cycle) or Docetaxel 75 mg/m^2 once every 3 weeks (Days 1 of a 3 week cycle) for 24 weeks followed by TYKERB 1500 mg once daily, or trastuzumab once weekly (loading dose 4m/kg followed by 2 mg/kg weekly infusions) plus Paclitaxel: 80 mg/m^2 once weekly (Days 1, 8 and 15 of a 4-week cycle) or Docetaxel 75 mg/m^2 once every 3 weeks (Days 1 of a 3 week cycle) for 24 weeks followed by trastuzumab: 6 mg/kg once every 3 weeks. The study was stopped when a pre-planned interim analysis showed that the trastuzumab arm was superior to the TYKERB arm. This was confirmed by the final analysis (see Table 14).

Table 14 Summary of Progression-Free Survival (PFS) and Overall Survival (OS) in Study EGF108919

	TYKERB plus taxane	Trastuzumab plus taxane
Progression Free Survival (ITT Population)	**(N=326)**	**(N=326)**
Median PFS1, months (95% CI)	**8.9 (0.30 - 32.69)**	**11.3 (0.30 - 38.54)**
Hazard Ratio (95% CI)	1.367 (1.133, 1.648)	
P value	0.0010	
Overall Survival (ITT Population)	**(N=326)**	**(N=326)**
Died	31%	25%
Hazard ratio, 95% CI (p value)	1.227 (0.946, 1.722) 0.1093	

Abbreviations: CI=confidence interval.

a Stratified HR for LTax/L versus TTax/T

Combination treatment with TYKERB and letrozole

Study EGF30008

TYKERB has been studied in combination with letrozole for the treatment of advanced or metastatic breast cancer in hormone receptor positive (oestrogen receptor [ER] positive and / or progesterone receptor [PgR] positive) postmenopausal women.

EGF30008 was a randomised, double-blind, controlled trial in patients with hormone-sensitive (HS) locally advanced or metastatic breast cancer (MBC), who had not received prior therapy for their metastatic disease. A total of 1286 patients were randomised to letrozole 2.5 mg once daily plus TYKERB 1500 mg once daily or letrozole 2.5 mg with placebo. Randomisation was stratified by sites of disease and prior adjuvant anti-oestrogen therapy. HER2 receptor status was retrospectively determined by central laboratory testing.

Of all patients randomised to treatment, 219 patients had tumours overexpressing the HER2 receptor (the 'HER2-positive population'), which was the pre-specified primary population for the analysis of efficacy. There were 952 HER2 negative patients and a total of 115 patients whose HER2 status was unconfirmed.

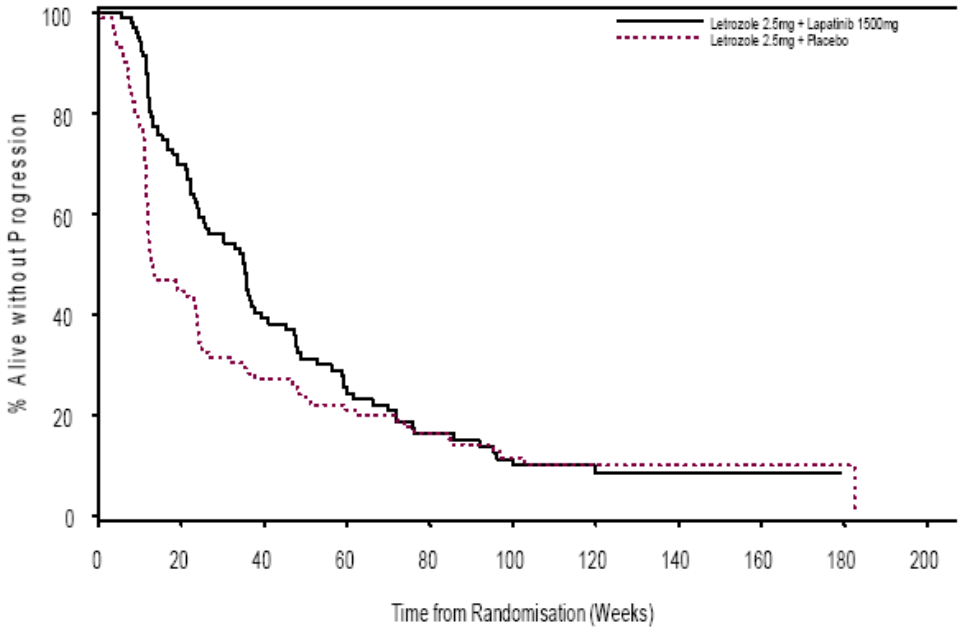
In the HER2-positive population, investigator-determined progression-free survival (PFS) was significantly greater with letrozole plus TYKERB compared with letrozole plus placebo (see Table 15). The PFS data in the HER2-positive population is represented graphically in Figure 2.

Table 15 Progression Free Survival (PFS) data from Study EGF30008 (TYKERB / letrozole)

	Primary population		Secondary Populations			
	HER2-Positive Population		Intent-to-Treat Population		HER2-Negative Population	
	N = 111	N = 108	N = 642	N = 644	N = 478	N = 474
	TYKERB 1500 mg / day + Letrozole 2.5 mg / day	Letrozole 2.5 mg / day + placebo	TYKERB 1500 mg / day + Letrozole 2.5 mg / day	Letrozole 2.5 mg / day + placebo	TYKERB 1500 mg / day + Letrozole 2.5 mg / day	Letrozole 2.5 mg / day + placebo
Median PFS, weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	51.7 (47.6, 59.6)	47.0 (36.9, 50.9)	59.7 (48.6, 69.7)	58.3 (47.9, 62.0)
Hazard Ratio	0.71 (0.53, 0.96)		0.86 (0.76, 0.98)		0.90 (0.77, 1.05)	
p-value	0.019		0.026		0.188	

CI= confidence interval

Figure 2 Kaplan-Meier Estimates for Investigator-Evaluated PFS (Study EGF30008, HER2-positive Population



The benefit of TYKERB + letrozole on PFS in the HER2-positive population was confirmed in a pre-planned Cox regression analysis (HR = 0.65 (95 % CI: 0.47-0.89); p = 0.008). In addition to a PFS benefit seen in the HER2+ patient population, combination therapy of TYKERB and letrozole was associated with a significant improvement in objective response rate (27.9% and 14.8 % respectively) (p=0.021) and in Clinical Benefit rate (CBR; complete plus partial response plus stable disease for >6 months) (47.7% and 28.7% respectively) (p=0.003) compared with treatment with letrozole plus placebo. Although not yet mature, a trend towards a survival benefit was noted for the TYKERB/letrozole combination, HR= 0.77 (95%CI 0.52-1.14) p=0.185.

In the Intent-to-Treat (ITT) population, investigator-determined PFS was greater between the two treatment arms (see Table 16). Although statistically significant, the difference was not considered clinically relevant.

In the HER2-negative population (n = 952), the Kaplan-Meier analyses for PFS did not show a significant difference between the two treatment arms (see Table 16). However, the pre-planned Cox regression model taking into account a number of baseline covariates for PFS did show an improvement with the TYKERB plus letrozole combination. (HR = 0.77 (95 % CI 0.64-0.94) p=0.010). In addition, age (younger), performance status (0), baseline serum HER2 ECD (<15ng/ml), number of metastatic sites (<3) and prior adjuvant anti-oestrogen stratification (<6 months since discontinuation) were identified as being significant prognostic factors.

Growth factor upregulation occurs with anti-oestrogen or endocrine therapy resistance. Therefore, the treatment effect in the pre-defined trial strata of prior endocrine therapy was further analyzed (<6 months since discontinuation of endocrine therapy and ≥ 6 months since discontinuation of endocrine therapy / never having received endocrine therapy). Table 16 below describes the PFS in these two subgroups of the HER2 negative population. In addition to the PFS benefit of TYKERB/letrozole therapy in the < 6 months stratum, a benefit in CBR was also noted when compared with letrozole plus placebo (43.8 % and 31.7 % respectively).

Table 16 Efficacy Results for Two Subgroups of HER2-negative Population

	<6 months since prior endocrine therapy[1]		**≥6 months since prior endocrine therapy/never received[2]**	
	N = 200		**N = 752**	
	TYKERB 1500 mg/ day + Letrozole 2.5 mg/ day	**Letrozole 2.5 mg/ day + placebo**	**TYKERB 1500 mg/ day + Letrozole 2.5 mg/ day**	**Letrozole 2.5 mg/ day + placebo**
	N = 96	N =104	N = 382	N = 370
Median PFS, weeks (95% CI)	36.3 (21.9, 55.3)	13.3 (12.1, 23.7)	64.0 (58.3, 73.1)	65.3 (59.1, 74.3)
Hazard Ratio	0.78 (0.57, 1.07)		0.94 (0.79, 1.13)	

	<6 months since prior endocrine therapy[1] N = 200		≥6 months since prior endocrine therapy/never received[2] N = 752	
	TYKERB 1500 mg/ day + Letrozole 2.5 mg/ day	**Letrozole 2.5 mg/ day + placebo**	**TYKERB 1500 mg/ day + Letrozole 2.5 mg/ day**	**Letrozole 2.5 mg/ day + placebo**
	N = 96	N =104	N = 382	N = 370
P-value	0.117		0.522	

CI= confidence interval
1 months since discontinuation of endocrine therapy
2 months since discontinuation of endocrine therapy/never received

5.2 Pharmacokinetic properties

Absorption

The absorption of lapatinib following oral administration of TYKERB 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 (Cmax) of lapatinib are achieved approximately 4 hours after administration. Daily dosing of 1250 mg produces steady state geometric mean (95% confidence interval) Cmax values of 2.43 (1.57 to 3.77) µg/mL and AUC values of 36.2 (23.4 to 56) µg*hr/mL.

Daily dosing of 1500 mg lapatinib in combination with paclitaxel 175 mg/m^2 every three weeks produces steady state geometric mean (95% confidence interval) Cmax values of 5.31 (3.54 to 7.97) µg/mL and AUC values of 64.5 (43.3 to 96.2) µg*hr/mL.

Systemic exposure to lapatinib is increased when administered with food (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.5, INTERACTIONWITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION). Lapatinib AUC values were approximately 3- and 4-fold higher (Cmax approximately 2.5 and 3–fold higher) when administered with a low fat (5% fat [500 calories]) or 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 (ABCG2) and Pgp (ABCB1). Lapatinib has also been shown to inhibit Pgp (IC50 2.3 µg/mL), BCRP (IC50 0.014 µ g/mL) and the hepatic uptake transporter OATP 1B1(IC50 2.3 µg/mL), *in vitro* at clinically relevant concentrations. The clinical significance of these effects on the pharmacokinetics of other drugs or the pharmacological activity of other anti-cancer agents is not known. Lapatinib does not significantly inhibit the OAT or OCT renal transporters (*in vitro* IC50 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 variety of oxidated metabolites, none of which account for more than 14% of the dose recovered in the faeces or 10% of the lapatinib concentration in plasma.

Elimination

The half-life of lapatinib measured after single doses increases with increasing dose. However, daily dosing of TYKERB 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.

In vitro evaluation of drug interaction potential

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 (*in vitro* IC50 values were greater than or equal to 6.9 µg/mL).

Special Populations

Children

The pharmacokinetics of TYKERB in paediatric patients has not been established.

Elderly

See Section 4.2, DOSE AND METHOD OF ADMINISTRATION – Special populations: Elderly.

Gender

Gender does not appear to affect lapatinib pharmacokinetics. An examination of combined data, including > 300 females and > 450 males, suggests no obvious difference.

Race/ethnicity

The available study data indicates no obvious distinction related to race/ethnicity.

Patients with renal impairment

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

Patients with hepatic impairment

The pharmacokinetics of lapatinib were examined in subjects with moderate (n = 8) or severe (n = 4) hepatic impairment 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 drug. Dose reduction is recommended for patients with severe pre-existing hepatic impairment. In patients who develop severe hepatotoxicity while on therapy, TYKERB should be discontinued permanently (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION and Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Pharmacogenomics

Polymorphic variations in drug-metabolizing enzymes, transporters, receptors, and other proteins that might affect lapatinib pharmacokinetics have not been explored.

The HLA alleles DQA1*02:01 and DRB1*07:01 were associated with hepatotoxicity in a genetic sub study of a monotherapy trial with TYKERB (see Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hepatotoxicity).

5.3 Preclinical safety data

Lapatinib was studied in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib and precocious ossification) occurred in rats at the maternally toxic dose of 120 mg/kg/day (6.4 times the expected clinical exposure in humans given 1250 mg lapatinib and 2000 mg/m^2 capecitabine). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (6.5 % and 19 % of the expected clinical exposure in humans given 1250 mg lapatinib and 2000 mg/m^2 capecitabine, respectively) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased foetal body weights, and minor skeletal variations. In the rat pre- and postnatal development study, a decrease in pup survival occurred between birth and postnatal day 21 at doses of 60 mg/kg/day or higher (3.3 times the expected clinical exposure in humans given 1250 mg lapatinib and 2000 mg/m^2 capecitabine). The highest no-effect dose for this study was 20 mg/kg/day.

There were no effects on male or female rat gonadal function, mating, or fertility at doses up to 120 mg/kg/day (females) and up to 180 mg/kg/day (males) (6.4 and 2.3 times the expected clinical exposure in humans given 1250 mg lapatinib and 2000 mg/m^2 capecitabine, respectively).

Lapatinib was not clastogenic or mutagenic in a battery of assays including the Chinese hamster chromosome aberration assay, the Ames assay, human lymphocyte chromosome aberration assay and an *in vivo* rat bone marrow chromosome aberration assay.
In oral carcinogenicity studies with lapatinib, severe skin lesions were seen at the highest doses tested which produced exposures based on AUC up to 1.7-fold in mice and male rats, and up to 12-fold in female rats, compared to humans given 1250 mg of lapatinib and 2000 mg/m^2 capecitabine. There was no evidence of carcinogenicity in mice. In rats, the incidence of benign haemangioma of the mesenteric lymph nodes was higher in some groups than in concurrent controls but was within background range. There was also an increase in renal infarcts and papillary necrosis in female rats at exposures 6 and 8-fold compared to humans

given 1250 mg of lapatinib and 2000 mg/m^2 capecitabine. The relevance of these findings for humans is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TYKERB tablets contain microcrystalline cellulose, macrogol 400, polysorbate 80, sodium starch glycollate, povidone, titanium dioxide, hypromellose, magnesium stearate, iron oxide yellow (CI77492), iron oxide red (CI77491).

6.2 Incompatibilities

None Reported.

6.3 Shelf life

Bottle packs: 24 months from date of manufacture
Blister packs: 24 months from date of manufacture

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HPDE bottle packs of 30*, 70, 84*, 105*, or 140* tablets.
Blister packs of 70*, 84* or 168* tablets.

*Not all pack sizes and container types are distributed in New Zealand

6.6 Special precautions for disposal

Any unused medicine should be returned to a pharmacist for safe disposal.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Novartis New Zealand Limited
PO Box 99102
Newmarket
Auckland 1149

Telephone: 0800 354 335

9 DATE OF FIRST APPROVAL

The date of publication in the New Zealand Gazette of consent to distribute the medicine: 24 January 2013.

10 DATE OF REVISION OF THE TEXT

23 August 2021

SUMMARY TABLE OF CHANGES

Section Changed	**Summary of New Information**
4.8	Addition of post-market AE “skin fissures” with frequency “common” based on pooled trial data
5.1	Revision of ATC code and Pharmacotherapeutic group