ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tyverb 250 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Oval, biconvex, yellow film-coated tablets, with “GS XJG” debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tyverb is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

- in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (see section 5.1).

- in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy (see section 5.1).

- in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor (see sections 4.4. and 5.1). No data are available on the efficacy of this combination relative to trastuzumab in combination with an aromatase inhibitor in this patient population.

4.2 Posology and method of administration

Tyverb treatment should only be initiated by a physician experienced in the administration of anti-cancer medicinal products.

HER2 (ErbB2) overexpressing tumours are defined by IHC3+, or IHC2+ with gene amplification or gene amplification alone. HER2 status should be determined using accurate and validated methods.

Posology

Tyverb / capecitabine combination posology

The recommended dose of Tyverb is 1250 mg (i.e. five tablets) once daily continuously.

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). Capecitabine should be taken with food or within 30 minutes after food. Please refer to the full prescribing information of capecitabine.

Tyverb / trastuzumab combination posology

The recommended dose of Tyverb is 1000 mg (i.e. four tablets) once daily continuously.

The recommended dose of trastuzumab is 4 mg/kg administered as an intravenous loading dose, followed by 2 mg/kg intravenous weekly (see section 5.1). Please refer to the full prescribing information of trastuzumab.

Tyverb / aromatase inhibitor combination posology

The recommended dose of Tyverb is 1500 mg (i.e. six tablets) once daily continuously.

Please refer to the full prescribing information of the co-administered aromatase inhibitor for dosing details.

Dose delay and dose reduction

Cardiac events

Tyverb should be discontinued in patients with symptoms associated with decreased left ventricular ejection fraction (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 (see section 4.4). Tyverb may be restarted at a reduced dose (750 mg/day when administered with trastuzumab, 1000 mg/day when administered with capecitabine or 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.

Interstitial lung disease / pneumonitis

Tyverb should be discontinued in patients who experience pulmonary symptoms which are NCI CTCAE grade 3 or greater (see section 4.4).

Diarrhoea

Tyverb 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) (see sections 4.4 and 4.8). Tyverb 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. Tyverb dosing should be permanently discontinued in patients with diarrhoea which is NCI CTCAE grade 4.

Other toxicities

Discontinuation or interruption of dosing with Tyverb may be considered when a patient develops toxicity greater than or equal to grade 2 on the NCI CTCAE. Dosing can be restarted, when the toxicity improves to grade 1 or less, at 1000 mg/day when administered with trastuzumab, 1250 mg/day when administered with capecitabine or 1500 mg/day when administered with an aromatase inhibitor. If the toxicity recurs, then Tyverb should be restarted at a lower dose (750 mg/day when administered with trastuzumab, 1000 mg/day when administered with capecitabine or 1250 mg/day when administered with an aromatase inhibitor).

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Caution is advised in patients with severe renal impairment as there is no experience of Tyverb in this population

(see section 5.2).

Hepatic impairment

Tyverb should be discontinued if changes in liver function are severe and patients should not be retreated (see section 4.4).

Administration of Tyverb to patients with moderate to severe hepatic impairment should be undertaken with caution due to increased exposure to the medicinal product. Insufficient data are available in patients with hepatic impairment to provide a dose adjustment recommendation (see section 5.2).

Elderly

There are limited data on the use of Tyverb / capecitabine and Tyverb / trastuzumab in patients aged ≥ 65 years.

In the phase III clinical study of Tyverb in combination with letrozole, of the total number of hormone receptor positive metastatic breast cancer patients (Intent to treat population N= 642), 44 % were ≥ 65 years of age. No overall differences in efficacy and safety of the combination of Tyverb and letrozole were observed between these patients and patients < 65 years of age.

Paediatric population

The safety and efficacy of Tyverb in children below the age of 18 years have not yet been established. No data are available.

Method of administration

Tyverb is for oral use.

The daily dose of Tyverb should not be divided. Tyverb should be taken either at least one hour before, or at least one hour after food. To minimise variability in the individual patient, administration of Tyverb should be standardised in relation to food intake, for example always to be taken one hour before a meal (see sections 4.5 and 5.2 for information on absorption).

Missed doses should not be replaced and the dosing should resume with the next scheduled daily dose (see section 4.9).

The full prescribing information of the co-administered medicinal product should be consulted for relevant details of their posology including any dose reductions, contraindications and safety information.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Data have shown that Tyverb combined with chemotherapy is less effective than trastuzumab when combined with chemotherapy.

Cardiac toxicity

Lapatinib has been associated with reports of decreases in LVEF (see section 4.8). Lapatinib has not been evaluated in patients with symptomatic cardiac failure. Caution should be taken if Tyverb is to be administered to patients with conditions that could impair left ventricular function (including co-

administration with potentially cardiotoxic medicinal products). Evaluation of cardiac function, including LVEF determination, should be conducted for all patients prior to initiation of treatment with Tyverb 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 Tyverb to ensure that LVEF does not decline to an unacceptable level (see section 4.2). In some cases, LVEF decrease may be severe and lead to cardiac failure. Fatal cases have been reported, causality of the deaths is uncertain. In studies across the clinical development programme for lapatinib, cardiac events including LVEF decreases were reported in approximately 1% of patients. Symptomatic LVEF decreases were observed in approximately 0.3% of patients who received lapatinib. However, when lapatinib was administered in combination with trastuzumab in the metastatic setting, the incidence of cardiac events including LVEF decreases was higher (7%) versus the lapatinib alone arm (2%) in the pivotal trial. The cardiac events observed in this study were comparable in nature and severity to those previously seen with lapatinib.

A concentration-dependent increase of the QTc interval was demonstrated in a dedicated placebo-controlled crossover study in subjects with advanced solid tumours.

Caution should be taken if Tyverb is administered to patients with conditions that could result in prolongation of QTc (including hypokalemia, hypomagnesemia, and congenital long QT syndrome), co-administration of other medicinal product known to cause QT prolongation, or conditions that increase the exposure of lapatinib, such as co-administration of strong CYP3A4 inhibitors. Hypokalemia or hypomagnesemia should be corrected prior to treatment. Electrocardiograms with QT measurement should be performed prior to and one to two weeks after the start of Tyverb therapy. When clinically indicated, e.g. after initiation of a concomitant treatment that might affect QT or that may interact with lapatinib, ECG measurement should also be considered.

Interstitial lung disease and pneumonitis

Lapatinib has been associated with reports of pulmonary toxicity including interstitial lung disease and pneumonitis (see section 4.8). Patients should be monitored for symptoms of pulmonary toxicity (dyspnoea, cough, fever) and treatment discontinued in patients who experience symptoms which are NCI CTCAE grade 3 or greater. Pulmonary toxicity may be severe and lead to respiratory failure. Fatal cases have been reported, causality of the deaths is uncertain.

Hepatotoxicity

Hepatotoxicity has occurred with Tyverb use and may in rare cases be fatal. The hepatotoxicity may occur days to several months after initiation of treatment. At the initiation of treatment, patients should be advised of the potential for hepatotoxicity. Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before the initiation of treatment and monthly thereafter, or as clinically indicated. Tyverb dosing should be discontinued if changes in liver function are severe and patients should not be retreated. Patients who carry the HLA alleles DQA1*02:01 and DRB1*07:01 have increased risk of Tyverb-associated hepatotoxicity. In a large, randomised clinical trial of Tyverb monotherapy (n=1,194), the cumulative frequency of severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE grade 3) at 1 year of treatment was 2.8% overall. The cumulative frequency in DQA1*02:01 and DRB1*07:01 allele carriers was 10.3% and in non-carriers was 0.5%. Carriage of the HLA risk alleles is common (15 to 25%) in Caucasian, Asian, African and Hispanic populations but lower (1%) in Japanese populations.

Caution is warranted if Tyverb is prescribed to patients with moderate or severe hepatic impairment and to patients with severe renal impairment (see sections 4.2 and 5.2).

Diarrhoea

Diarrhoea, including severe diarrhoea, has been reported with Tyverb treatment (see section 4.8). Diarrhoea can be potentially life-threatening if accompanied by dehydration, renal insufficiency, neutropenia and/or electrolyte imbalances and fatal cases have been reported. Diarrhoea generally

occurs early during Tyverb treatment, with almost half of those patients with diarrhoea first experiencing it within 6 days. This usually lasts 4-5 days. Tyverb-induced diarrhoea is usually low-grade, with severe diarrhoea of NCI CTCAE grades 3 and 4 occurring in <10% and <1% of patients, respectively. At the start of therapy, the patients bowel pattern and any other symptoms (e.g. fever, cramping pain, nausea, vomiting, dizziness and thirst) should be determined, to allow identification of changes during treatment and to help identify patients at greater risk of diarrhoea. Patients should be instructed to promptly report any change in bowel patterns. In potentially severe cases of diarrhoea the measuring of neutrophil counts and body temperature should be considered. Proactive management of diarrhoea with anti-diarrhoeal medicinal product is important. 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 Tyverb therapy (see section 4.2 – dose delay and dose reduction –diarrhoea).

Serious cutaneous reactions

Serious cutaneous reactions have been reported with Tyverb. 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 Tyverb.

Concomitant treatment with inhibitors or inducers of CYP3A4

Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to lapatinib (see section 4.5).

Concomitant treatment with strong inhibitors of CYP3A4 should be avoided due to risk of increased exposure to lapatinib (see section 4.5).

Grapefruit juice should be avoided during treatment with Tyverb (see section 4.5).

Co-administration of Tyverb with orally administered medicinal products with narrow therapeutic windows that are substrates of CYP3A4 and /or CYP2C8 should be avoided (see section 4.5).

Concomitant treatment with substances that increase gastric pH should be avoided, as lapatinib solubility and absorption may decrease (see section 4.5).

Tyverb contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on lapatinib

Lapatinib is predominantly metabolised by CYP3A (see section 5.2).

In healthy volunteers receiving ketoconazole, a strong CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure to lapatinib (100 mg daily) was increased approximately 3.6–fold, and half-life increased 1.7–fold. Co-administration of Tyverb with strong inhibitors of CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone) should be avoided. Co-administration of Tyverb with moderate inhibitors of CYP3A4 should proceed with caution and clinical adverse reactions should be carefully monitored.

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 Tyverb with known inducers of CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or Hypericum perforatum [St John's Wort]) should be avoided.

Lapatinib is a substrate for the transport proteins Pgp and BCRP. Inhibitors (ketoconazole, itraconazole, quinidine, verapamil, cyclosporine, and erythromycin) and inducers (rifampicin and St John's Wort) of these proteins may alter the exposure and/or distribution of lapatinib (see section 5.2).

The solubility of lapatinib is pH-dependent. Concomitant treatment with substances that increase gastric pH should be avoided, as lapatinib solubility and absorption may decrease. Pre-treatment with a proton pump inhibitor (esomeprazole) decreased lapatinib exposure by an average of 27% (range: 6% to 49%). This effect decreases with increasing age from approximately 40 to 60 years.

Effects of lapatinib on other medicinal products

Lapatinib inhibits CYP3A4 *in vitro* at clinically relevant concentrations. Co-administration of Tyverb 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. Co-administration of Tyverb with orally administered medicinal products with narrow therapeutic windows that are substrates of CYP3A4 (e.g. cisapride, pimozide and quinidine) should be avoided (see sections 4.4 and 5.2).

Lapatinib inhibits CYP2C8 *in vitro* at clinically relevant concentrations. Co-administration of Tyverb with medicinal products with narrow therapeutic windows that are substrates of CYP2C8 (e.g. repaglinide) should be avoided (see sections 4.4 and 5.2).

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

Co-administration of lapatinib with intravenously administered docetaxel did not significantly affect the AUC or C_{max} of either active substance. However, the occurrence of docetaxel-induced neutropenia was increased.

Co-administration of Tyverb 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, but it is assumed to be due to inhibition of one or more transport proteins by lapatinib. Adverse reactions should be carefully monitored if Tyverb is co-administered with irinotecan, and a reduction in the dose of irinotecan should be considered.

Lapatinib inhibits the transport protein Pgp *in vitro* at clinically relevant concentrations. Co-administration of lapatinib with orally administered digoxin resulted in an approximate 80% increase in the AUC of digoxin. Caution should be exercised when dosing lapatinib concurrently with medicinal products with narrow therapeutic windows that are substrates of Pgp, and a reduction in the dose of the Pgp substrate should be considered.

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) and OATP1B1 (e.g. rosuvastatin) (see section 5.2).

Concomitant administration of Tyverb with capecitabine, letrozole or trastuzumab did not meaningfully alter the pharmacokinetics of these medicinal products (or the metabolites of capecitabine) or lapatinib.

Interactions with food and drink

The bioavailability of lapatinib is increased up to about 4 times by food, depending on e.g. the fat

content in the meal. Furthermore, depending on type of food the bioavailability is approximately 2-3 times higher when lapatinib is taken 1 hour after food compared with 1 hour before the first meal of the day (see sections 4.2 and 5.2).

Grapefruit juice may inhibit CYP3A4 in the gut wall and increase the bioavailability of lapatinib and should therefore be avoided during treatment with Tyverb.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with Tyverb and for at least 5 days after the last dose.

Pregnancy

There are no adequate data from the use of Tyverb in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is not known.

Tyverb should not be used during pregnancy unless clearly necessary.

Breast-feeding

The safe use of Tyverb during breast-feeding has not been established. It is not known whether lapatinib is excreted in human milk. In rats, growth retardation was observed in pups which were exposed to lapatinib via breast milk. Breast-feeding must be discontinued in women who are receiving therapy with Tyverb and for at least 5 days after the last dose.

Fertility

There are no adequate data from the use of Tyverb in women of childbearing potential.

4.7 Effects on ability to drive and use machines

Tyverb has no influence on the ability to drive and use machines. A detrimental effect on such activities cannot be predicted from the pharmacology of lapatinib. The clinical status of the patient and the safety profile of lapatinib 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

The safety of lapatinib has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 20,000 patients, including 198 patients who received lapatinib in combination with capecitabine, 149 patients who received lapatinib in combination with trastuzumab and 654 patients who received lapatinib in combination with letrozole (see section 5.1).

The most common adverse reactions (>25%) during therapy with lapatinib were gastrointestinal events (such as diarrhoea, nausea, and vomiting) and rash. Palmar-plantar erythrodysesthesia (PPE) was also common (>25%) when lapatinib was administered in combination with capecitabine. The incidence of PPE was similar in the lapatinib plus capecitabine and capecitabine alone treatment arms. Diarrhoea was the most common adverse reaction resulting in discontinuation of treatment when lapatinib was administered in combination with capecitabine, or with letrozole.

No additional adverse reactions were reported to be associated with lapatinib in combination with trastuzumab. There was an increased incidence of cardiac toxicity, but these events were comparable

in nature and severity to those reported from the lapatinib clinical programme (see section 4.4 – cardiac toxicity). These data are based on exposure to this combination in 149 patients in the pivotal trial.

Tabulated list of adverse reactions

The following adverse reactions have been reported to have a causal association with lapatinib alone or lapatinib in combination with capecitabine, trastuzumab or letrozole.

The following convention has been utilised for the classification of frequency: very common ((≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders	
Rare	Hypersensitivity reactions including anaphylaxis (see section 4.3)
Metabolism and nutrition disorders	
Very common	Anorexia
Psychiatric disorders	
Very common	Insomnia*
Nervous system disorders	
Very common	Headache†
Common	Headache*
Cardiac disorders	
Common	Decreased left ventricular ejection fraction (see section 4.2 - dose reduction – cardiac events and section 4.4).
Not known	Ventricular arrhythmias/Torsades de Pointes, electrocardiogram QT prolonged**
Vascular disorders	
Very common	Hot flush†
Respiratory, thoracic and mediastinal disorders	
Very common	Epistaxis†, cough†, dyspnoea†.
Uncommon	Interstitial lung disease/pneumonitis.
Not known	Pulmonary arterial hypertension**.
Gastrointestinal disorders	
Very common	Diarrhoea, which may lead to dehydration (see section 4.2 - dose delay and dose reduction – other toxicities and section 4.4), nausea, vomiting, dyspepsia*, stomatitis*, constipation*, abdominal pain*.
Common	Constipation†
Hepatobiliary disorders	
Common	Hyperbilirubinaemia, hepatotoxicity (see section 4.4).
Skin and subcutaneous tissue disorders	
Very common	Rash (including dermatitis acneiform) (see section 4.2 - dose delay and dose reduction – other toxicities), dry skin*†, palmar-plantar erythrodysaesthesia*, alopecia†, pruritus†.
Common	Nail disorders including paronychia, skin fissures.
Not known	Serious cutaneous reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)**
Musculoskeletal and connective tissue disorders	
Very common	Pain in extremity*†, back pain*†, arthralgia†.
General disorders and administration site conditions	
Very common	Fatigue, mucosal inflammation*, asthenia†.

* These adverse reactions were observed when lapatinib was administered in combination with capecitabine.

† These adverse reactions were observed when lapatinib was administered in combination with

letrozole.

** Adverse reactions from spontaneous reports and literature

Description of selected adverse reactions

Decreased left ventricular ejection fraction and QT interval prolongation

Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 1% of patients receiving lapatinib and were asymptomatic in more than 70% of cases. LVEF decreases resolved or improved in more than 70 % of cases, in approximately 60 % of these on discontinuation of treatment with lapatinib, and in approximately 40 % of cases lapatinib was continued. Symptomatic LVEF decreases were observed in approximately 0.3% of patients who received lapatinib monotherapy or in combination with other anti-cancer medicinal products. Observed adverse reactions included dyspnoea, cardiac failure and palpitations. Overall 58 % of these symptomatic patients recovered. LVEF decreases were reported in 2.5 % of patients who received lapatinib in combination with capecitabine, as compared to 1.0 % with capecitabine alone. LVEF decreases were reported in 3.1 % of patients who received lapatinib in combination with letrozole as compared to 1.3 % of patients receiving letrozole plus placebo. LVEF decreases were reported in 6.7 % of patients who received lapatinib in combination with trastuzumab, as compared to 2.1 % of patients who received lapatinib alone.

A concentration dependent increase in QTcF (maximum mean ΔΔQTcF 8.75 ms; 90% CI 4.08, 13.42) was observed in a dedicated QT study in patients with advanced solid tumours (see section 4.4).

Diarrhoea

Diarrhoea occurred in approximately 65 % of patients who received lapatinib in combination with capecitabine, in 64 % of patients who received lapatinib in combination with letrozole and in 62 % of patients who received lapatinib in combination with trastuzumab. Most cases of diarrhoea were grade 1 or 2 and did not result in discontinuation of treatment with lapatinib. Diarrhoea responds well to proactive management (see section 4.4). However, a few cases of acute renal failure have been reported secondary to severe dehydration due to diarrhoea.

Rash

Rash occurred in approximately 28 % of patients who received lapatinib in combination with capecitabine, in 45 % of patients who received lapatinib in combination with letrozole and in 23 % of patients who received lapatinib in combination with trastuzumab. Rash was generally low grade and did not result in discontinuation of treatment with lapatinib. Prescribing physicians are advised to perform a skin examination prior to treatment and regularly during treatment. Patients experiencing skin reactions should be encouraged to avoid exposure to sunlight and apply broad spectrum sunscreens with a Sun Protection Factor (SPF) ≥ 30. If a skin reaction occurs a full body examination should be performed at every visit until one month after resolution. Patients with extensive or persistent skin reactions should be referred to a dermatologist.

Hepatotoxicity

The risk of lapatinib-induced hepatotoxicity was associated with carriage of the HLA alleles DQA1*02:01 and DRB1*07:01 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

Asymptomatic and symptomatic cases of overdose have been reported in patients being treated with Tyverb. In patients who took up to 5000 mg of lapatinib, symptoms observed include known lapatinib associated events (see section 4.8) and in some cases sore scalp and/or mucosal inflammation. In a single case of a patient who took 9000 mg of Tyverb, sinus tachycardia (with otherwise normal ECG) was also observed.

Lapatinib 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, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors, ATC code: L01EH01.

Mechanism of action

Lapatinib, a 4-anilinoquinazoline, is an inhibitor of the intracellular tyrosine kinase domains of both EGFR (ErbB1) and of HER2 (ErbB2) receptors (estimated Ki^{app} values of 3nM and 13nM, 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.

The combination of lapatinib and trastuzumab may offer complementary mechanisms of action as well as possible non-overlapping mechanisms of resistance. The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against HER2-amplified breast cancer cell lines selected for long-term growth in trastuzumab-containing medium *in vitro* and was synergistic in combination with trastuzumab in these cell lines.

Clinical efficacy and safety

Combination treatment with Tyverb and capecitabine

The efficacy and safety of Tyverb in combination with capecitabine in breast cancer patients with good performance status was evaluated in a randomised, phase III study. Patients eligible for enrolment had HER2-overexpressing, locally advanced or metastatic breast cancer, progressing after prior treatment that included taxanes, anthracyclines and trastuzumab. LVEF was evaluated in all patients (using echocardiogram [Echo] or multi gated acquisition scan [MUGA]) prior to initiation of treatment with Tyverb to ensure baseline LVEF was within the institutions normal limits. In the clinical study LVEF was monitored at approximately eight week intervals during treatment with Tyverb to ensure it did not decline to below the institutions lower limit of normal. The majority of LVEF decreases (greater than 60 % of events) were observed during the first nine weeks of treatment, however limited data was available for long term exposure.

Patients were randomised to receive either Tyverb 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). The primary endpoint was time to progression (TTP). Assessments were undertaken by the study investigators and by an independent review panel, blinded to treatment. The study was halted based on the results of a pre-specified interim analysis that showed an improvement in TTP for patients receiving Tyverb plus capecitabine. An additional 75 patients were enrolled in the study between the time of the interim analysis and the end of the enrolment. Investigator analysis on data at the end of enrolment is presented in Table 1.

Table 1 Time to progression data from Study EGF100151 (Tyverb / capecitabine)

	Investigator assessment	
	Tyverb (1250 mg/day)+ capecitabine (2000 mg/m^2/day, days 1-14 q21 days)	**Capecitabine (2500 mg/m^2/day, days 1-14 q21 days)**
	(N = 198)	**(N = 201)**
Number of TTP events	121	126
Median TTP, weeks	23.9	18.3
Hazard Ratio	0.72	
(95% CI)	(0.56, 0.92)	
p value	0.008	

The independent assessment of the data also demonstrated that Tyverb when given in combination with capecitabine significantly increased time to progression (Hazard Ratio 0.57 [95 % CI 0.43, 0.77] p=0.0001) compared to capecitabine alone.

Results of an updated analysis of the overall survival data to 28 September 2007 are presented in Table 2.

Table 2 Overall survival data from Study EGF100151 (Tyverb / capecitabine)

	Tyverb (1250 mg/day)+ capecitabine (2000 mg/m^2/day, days 1-14 q21 days)	**Capecitabine (2500 mg/m^2/day, days 1-14 q21 days)**
	(N = 207)	**(N = 201)**
Number of subjects who died	148	154
Median overall survival, weeks	74.0	65.9
Hazard Ratio	0.9	
(95% CI)	(0.71, 1.12)	
p value	0.3	

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.

Data are available on the efficacy and safety of Tyverb in combination with capecitabine relative to trastuzumab in combination with capecitabine. A randomised Phase III study (EGF111438) (N=540) compared the effect of the two regimens on the incidence of CNS as site of first relapse in women with HER2 overexpressing metastatic breast cancer. Patients were randomised to either Tyverb 1250 mg once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or trastuzumab (loading dose of 8mg/kg followed by 6mg/kg q3 weekly infusions) plus capecitabine (2500mg/m^2/day, days 1-14, every 21 days). Randomisation was stratified by prior trastuzumab treatment and number of prior treatments for metastatic disease. The study was halted as the interim analysis (N=475) showed a low incidence of CNS events and, superior efficacy of the trastuzumab plus capecitabine arm in terms of progression-free survival and overall survival (see results of final analysis in Table 3).

In the Tyverb plus capecitabine arm 8 patients (3.2%) experienced CNS as site of first progression, compared with 12 patients (4.8%) in the trastuzumab plus capecitabine arm.

Lapatinib effect on CNS metastasis

Lapatinib has in terms of objective responses demonstrated modest activity in the treatment of established CNS metastases. In the prevention of CNS metastases in the metastatic and early breast cancer settings the observed activity was limited.

Table 3 Analyses of investigator-assessed progression-free survival and overall survival

	Investigator-assessed PFS		**Overall survival**	
	Tyverb (1250 mg/day) + capecitabine (2000 mg/m²/day, days 1-14 q21 days)	**Trastuzumab (loading dose of 8mg/kg followed by 6mg/kg q3 weekly infusions) + capecitabine (2500 mg/m²/day, days 1-14 q21 days)**	**Tyverb (1250 mg/day) + capecitabine (2000 mg/m²/day, days 1-14 q21 days)**	**Trastuzumab (loading dose of 8mg/kg followed by 6mg/kg q3 weekly infusions) + capecitabine (2500 mg/m²/day, days 1-14 q21 days)**
ITT population				
N	271	269	271	269
Number (%) with event[1]	160 (59)	134 (50)	70 (26)	58 (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	
Subjects who had received prior trastuzumab*				
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)	
Subjects 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 lower risk for Tyverb 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.
* Post hoc analysis

Combination treatment with Tyverb and trastuzumab

The efficacy and safety of lapatinib in combination with trastuzumab in metastatic breast cancer were evaluated in a randomised trial. Eligible patients were women with Stage IV ErbB2 gene amplified (or protein overexpressing) metastatic breast cancer who had been exposed to treatment with anthracyclines and taxanes. In addition, per the protocol, patients were to be reported by the investigators as having progressed on their most recent trastuzumab containing regimen in the metastatic setting. The median number of prior trastuzumab-containing regimens was three. Patients were randomised to receive either oral lapatinib 1000 mg once daily plus trastuzumab 4 mg/kg administered as an intravenousloading dose, followed by 2 mg/kg intravenous weekly (N = 148), or oral lapatinib 1500 mg once daily (N = 148). Patients who had objective disease progression after receiving at least 4 weeks of treatment with lapatinib monotherapy were eligible to crossover to combination therapy. Of the 148 patients who received monotherapy treatment, 77 (52%) patients elected at the time of disease progression to receive combination treatment.

Progression-free survival (PFS) was the primary endpoint of the study with response rate and overall survival (OS) as secondary endpoints. The median age was 51 years and 13% were 65 years or older. Ninety-four percent (94%) were Caucasian. Most patients in both treatment arms had visceral disease (215 [73%] patients overall). In addition, 150 [50%] of patients were hormone receptor negative. A summary of efficacy endpoints and overall survival data is provided in Table 4. Subgroup analysis results based on predefined stratification factor (hormone receptor status) is also shown in Table 5.

Table 4 Progression-free survival and overall survival data (Tyverb / trastuzumab)

	Lapatinib plus trastuzumab (N=148)	**Lapatinib alone (N=148)**
Median PFS[1], weeks (95% CI)	12.0 (8.1, 16.0)	8.1 (7.6, 9.0)
Hazard ratio (95% CI)	0.73 (0.57, 0.93)	
***P* value**	0.008	
Response rate, % (95% CI)	10.3 (5.9, 16.4)	6.9 (3.4, 12.3)
Died	105	113
Median overall survival[1], months (95% CI)	14.0 (11.9, 17.2)	9.5 (7.6, 12.0)
Hazard ratio (95% CI)	0.74 (0.57, 0.97)	
***P* value**	0.026	

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

Table 5 Summary of PFS and OS in studies with hormone receptor negative

	Median PFS	**Median OS**
Lap+Tras	15.4 wks (8.4, 16.9)	17.2 mos (13.9, 19.2)
Lap	8.2 wks (7.4, 9.3)	8.9 mos (6.7, 11.8)
HR (95% CI)	0.73 (0.52, 1.03)	0.62 (0.42, 0.90)

Combination treatment with Tyverb and letrozole

Tyverb has been studied in combination with letrozole for the treatment of postmenopausal women with hormone receptor-positive (oestrogen receptor [ER] positive and / or progesterone receptor [PgR]

positive) advanced or metastatic breast cancer.

The Phase III study (EGF30008) was randomised, double-blind, and placebo controlled. The study enrolled patients who had not received prior therapy for their metastatic disease.

In the HER2-overexpressing population, only 2 patients were enrolled who had received prior trastuzumab, 2 patients had received prior aromatase inhibitor therapy, and approximately half had received tamoxifen.

Patients were randomised to letrozole 2.5 mg once daily plus Tyverb 1500 mg once daily or letrozole with placebo. Randomisation was stratified by sites of disease and by time from discontinuation of 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, and this was the pre-specified primary population for the analysis of efficacy. There were 952 patients with HER2-negative tumours, and a total of 115 patients whose tumour HER2 status was unconfirmed (no tumour sample, no assay result, or other reason).

In patients with HER2-overexpressing MBC, investigator-determined progression-free survival (PFS) was significantly greater with letrozole plus Tyverb compared with letrozole plus placebo. In the HER2-negative population, there was no benefit in PFS when letrozole plus Tyverb was compared with letrozole plus placebo (see Table 6).

Table 6 Progression free survival data from Study EGF30008 (Tyverb / letrozole)

	HER2-overexpressing population		**HER2-negative population**	
	N = 111	**N = 108**	**N = 478**	**N = 474**
	Tyverb 1500 mg / day + Letrozole 2.5 mg /day	**Letrozole 2.5 mg /day + placebo**	**Tyverb 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)	59.7 (48.6, 69.7)	58.3 (47.9, 62.0)
Hazard ratio	0.71 (0.53, 0.96)		0.90 (0.77, 1.05)	
P-value	0.019		0.188	
Objective response rate (ORR)	27.9%	14.8%	32.6%	31.6%
Odds ratio	0.4 (0.2, 0.9)		0.9 (0.7, 1.3)	
P-value	0.021		0.26	
Clinical benefit rate (CBR)	47.7%	28.7%	58.2%	31.6%
Odds ratio	0.4 (0.2, 0.8)		1.0 (0.7, 1.2)	
P-value	0.003		0.199	

CI= confidence interval
HER2 overexpression = IHC 3+ and/or FISH positive; HER2 negative = IHC 0, 1+ or 2+ and/or FISH negative
Clinical benefit rate was defined as complete plus partial response plus stable disease for ≥6 months.

At the time of the final PFS analysis (with median follow-up of 2.64 years), the overall survival data were not mature and there was no significant difference between treatment groups in the HER2-positive population; this had not changed with additional follow-up (>7.5 years median follow-up time; Table 7).

Table 7 Overall survival (OS) results from study EGF30008 (in the HER2-positive population only)

	Tyverb 1500 mg / day + Letrozole 2.5 mg /day N=111	**Letrozole 2.5 mg /day + placebo N=108**
Pre-planned OS analysis (conducted at the time of the final PFS analysis, 03 June 2008)		
Median follow-up (yrs)	2,64	2,64
Deaths (%)	50 (45)	54 (50)
Hazard ratio[a] (95% CI), p-value[b]	0,77 (0,52; 1,14); 0,185	
Final OS analysis (post-hoc analysis, 07 August 2013)		
Median follow-up (yrs)	7,78	7,55
Deaths (%)	86 (77)	78 (72)
Hazard ratio (95% CI), p-value	0,97 (0,07; 1,33); 0,848	

Median values from Kaplan-Meier analysis; HR and p-values from Cox regression models adjusting for important prognostic factors.

a. Estimate of the treatment hazard ratio, where <1 indicates a lower risk with letrozole 2.5 mg + lapatinib 1500 mg compared with letrozole 2.5 mg + placebo.
b. P-value from Cox regression model, stratifying for site of disease and prior anti-adjuvant therapy at screening.

Cardiac electrophysiology

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 tumours (EGF114271) (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 electrocardiograms (ECGs) and pharmacokinetic samples, were taken 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 pharmacodynamics 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 2000 mg).

There is a positive relationship between lapatinib plasma concentrations and ΔΔQTcF. Lapatinib produced a maximum mean concentration of 3920 (3450-4460) ng/ml (geometric mean/95% CI), exceeding the geometric mean $C_{max.ss}$ and 95% CI values observed following the approved dosing regimens. An additional increase in peak exposure of lapatinib can be expected when lapatinib is taken repeatedly with food (see sections 4.2 and 5.2) or concomitantly with strong CYP3A4 inhibitors. When lapatinib is taken in combination with strong CYP3A4 inhibitors the QTc interval can be expected to be prolonged by 16.1 ms (12.6-20.3 ms) as demonstrated in a model-based prediction (see section 4.4).

Food effects on lapatinib exposure

The bioavailability and thereby the plasma concentrations of lapatinib are increased by food, in relation to the content and timing of the meal. Dosing of lapatinib one hour after a meal results in approximately 2-3 times higher systemic exposure, compared to dosing one hour before a meal (see sections 4.5 and 5.2).

The European Medicines Agency has waived the obligation to submit the results of studies with Tyverb in all subsets of the paediatric population in the treatment of breast carcinoma (see section 4.2

for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability following oral administration of lapatinib is unknown, but it is incomplete and variable (approximately 70% 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 1250 mg produces steady state geometric mean (coefficient of variation) C_{max} values of 2.43 (76%) µg/ml and AUC values of 36.2 (79%) 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, as compared with administration in the fasted state. Systemic exposure to lapatinib is also affected by the timing of administration in relation to food intake. Relative to dosing 1 hour before a low fat breakfast, mean AUC values were approximately 2- and 3-fold higher when lapatinib was administered 1 hour after a low fat or high fat 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 (ABCB1). Lapatinib has also been shown *in vitro* to inhibit these efflux transporters, as well as the hepatic uptake transporter OATP 1B1, at clinically relevant concentrations (IC_{50} values were equal to 2.3 µg/ml). The clinical significance of these effects on the pharmacokinetics of other medicinal products or the pharmacological activity of other anti-cancer medicinal products is not known.

Biotransformation

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).

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. Biliary excretion may also contribute to the elimination. The primary route of excretion for lapatinib and its metabolites is in faeces. Recovery of unchanged lapatinib in faeces accounts for a median 27% (range 3 to 67%) of an oral dose. Less than 2% of the administered oral dose (as lapatinib and metabolites) excreted in urine.

Renal impairment

Lapatinib pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing haemodialysis. Available data suggest that no dose adjustment is necessary in patients with mild to moderate renal impairment.

Hepatic impairment

The pharmacokinetics of lapatinib were examined in patients 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 patients. Systemic exposure (AUC) to lapatinib after a single oral 100 mg dose increased approximately 56% and 85% in patients with moderate and severe hepatic impairment, respectively. Administration of lapatinib in patients with hepatic impairment should be undertaken with caution (see sections 4.2 and 4.4).

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 ≥60 mg/kg/day (4 times the expected human clinical exposure). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (8% and 23% of the expected human clinical exposure, respectively) and abortions at 120 mg/kg/day. At ≥60 mg/kg/day there were 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 (5 times the expected human clinical exposure). The highest no-effect dose for this study was 20 mg/kg/day.

In oral carcinogenicity studies with lapatinib, severe skin lesions were seen at the highest doses tested which produced exposures based on AUC up to 2-fold in mice and male rats, and up to 15-fold in female rats, compared to humans given 1250 mg of lapatinib once daily. 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. There was also an increase in renal infarcts and papillary necrosis in female rats at exposures 7 and 10-fold compared to humans given 1250 mg of lapatinib once daily. The relevance of these findings for humans is uncertain.

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) (8 and 3 times the expected human clinical exposure, respectively). The effect on human fertility is unknown.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate (Type A)
Magnesium stearate

Tablet coating

Hypromellose
Titanium dioxide (E171)
Macrogol (400)
Polysorbate 80
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister packs

2 years

Bottles

3 years

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Tyverb is supplied in either blister packs or bottles.

Blister packs

Tyverb / capecitabine combination posology
Each pack of Tyverb contains 70 film-coated tablets in foil blisters (polyamide / aluminium / polyvinyl chloride / aluminium) of 10 tablets each. Each foil has a perforation down the middle to allow the blisters to be separated into a daily dose of 5 tablets.

Multipacks contain 140 (2 packs of 70) film-coated tablets.

Tyverb / aromatase inhibitor combination posology
Each pack of Tyverb contains 84 film-coated tablets in foil blisters (polyamide / aluminium / polyvinyl chloride / aluminium) of 12 tablets each. Each foil has a perforation down the middle to allow the blisters to be separated into a daily dose of 6 tablets.

Bottles

Tyverb is also supplied in high density polyethylene bottles (HDPE) with a child resistant polypropylene closure containing 70, 84, 105 or 140 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/440/001-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2008
Date of latest renewal: 19 September 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Glaxo Wellcome S.A.
Avenida de Extremadura 3
09400 Aranda de Duero
Burgos
Spain

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharmaceuticals S.R.L.
Str. Livezeni nr. 7A
540472 Targu Mures
Romania

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation

and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (14 DAY, SINGLE PACK)

1. NAME OF THE MEDICINAL PRODUCT

Tyverb 250 mg film-coated tablets
lapatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

70 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/440/001 70 tablets
EU/1/07/440/003 84 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tyverb 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (28-DAY, MULTIPACK)

1. NAME OF THE MEDICINAL PRODUCT

Tyverb 250 mg film-coated tablets
lapatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

140 film-coated tablets
Multipack: 140 (2 packs of 70) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/440/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tyverb 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (14 DAY PACK, PART OF 28 DAY MULTIPACK without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Tyverb 250 mg film-coated tablets
lapatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

70 film-coated tablets

Component of a multipack, cannot to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/440/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tyverb 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Tyverb 250 mg tablets
lapatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Tyverb 250 mg film-coated tablets
lapatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

70 film-coated tablets
84 film-coated tablets
105 film-coated tablets
140 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/440/004	70 tablets
EU/1/07/440/005	140 tablets
EU/1/07/440/006	84 tablets
EU/1/07/440/007	105 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tyverb 250 mg [folding box only]

17. UNIQUE IDENTIFIER – 2D BARCODE

[folding box only]

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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B. PACKAGE LEAFLET

Package leaflet: Information for the user

Tyverb 250 mg film-coated tablets
lapatinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Don't pass it on to others. It may harm them, even if their signs of illness seem the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tyverb is and what it is used for
2. What you need to know before you take Tyverb
3. How to take Tyverb
4. Possible side effects
5. How to store Tyverb
6. Contents of the pack and other information

1. What Tyverb is and what it is used for

Tyverb is used to treat certain types of breast cancer *(HER2-overexpressing)* which have spread beyond the original tumour or to other organs (*advanced* or *metastatic* breast cancer). It may slow or stop cancer cells from growing, or may kill them.

Tyverb is prescribed to be taken in combination with another anti-cancer medicine.

Tyverb is prescribed in **combination with capecitabine**, for patients who have had treatment for advanced or metastatic breast cancer before. This previous treatment for metastatic breast cancer must have included trastuzumab.

Tyverb is prescribed in **combination with trastuzumab**, for patients who have hormone receptor-negative metastatic breast cancer and have had other treatment for advanced or metastatic breast cancer before.

Tyverb is prescribed in **combination with an aromatase inhibitor**, for patients with hormone sensitive metastatic breast cancer (breast cancer that is more likely to grow in the presence of hormones), who are not currently intended for chemotherapy.

Information about these medicines is described in separate patient information leaflets. **Ask your doctor** to give you information about these other medicines.

2. What you need to know before you take Tyverb

Do not take Tyverb
- if you are allergic to lapatinib or any of the other ingredients of this medicine (listed in Section 6).

Take special care with Tyverb

Your doctor will run tests to check that your heart is working properly before and during your

treatment with Tyverb.

Tell your doctor if you have any heart problems before you take Tyverb.

Your doctor also needs to know before you take Tyverb:
- if you have lung disease
- if you have inflammation of the lung
- if you have any **liver problems**
- if you have any **kidney problems**
- if you have diarrhoea (see section 4).

Your doctor will run tests to check that your liver is working properly before and during your treatment with Tyverb.

Tell your doctor if any of these apply to you.

Serious skin reactions
Serious skin reactions have been seen with Tyverb. Symptoms may include skin rash, blisters and skin peeling.

Tell your doctor as soon as possible if you get any of these symptoms.

Other medicines and Tyverb
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and other medicines you bought without a prescription.

It is especially important to tell your doctor if you are taking, or have recently taken any of the following medicines. Some medicines may affect the way Tyverb works or Tyverb may affect how other medicines work. These medicines include some medicines in the following groups:

- St John's Wort – a herb extract used to treat **depression**
- erythromycin, ketoconazole, itraconazole, posaconazole, voriconazole, rifabutin, rifampicin, telithromycin **–** medicines used to treat **infections**
- cyclosporine – a medicine used to **suppress the immune system** for example after organ transplantations
- ritonavir, saquinavir – medicines used to treat **HIV**
- phenytoin, carbamazepine – medicines used to treat **seizures**
- cisapride – a medicine used to treat certain **digestive system** problems
- pimozide – a medicine used to treat certain **mental health problems**
- quinidine, digoxin – medicines used to treat certain **heart problems**
- repaglinide – a medicine used to treat **diabetes**
- verapamil – a medicine used to treat **high blood pressure** or **heart problems** (*angina*)
- nefazodone – a medicine used to treat **depression**
- topotecan, paclitaxel, irinotecan, docetaxel – medicines used to treat certain types of **cancer**
- rosuvastatin – a medicine used to treat **high cholesterol**
- medicines that decrease stomach acidity - used to treat **stomach ulcers** or **indigestion**

Tell your doctor if you are taking, or have recently taken, any of these.

Your doctor will review the medicines you are currently taking to make sure you are not taking something that can't be taken with the Tyverb. Your doctor will advise you whether an alternative is available.

Tyverb with food and drink

Don't drink grapefruit juice while you are being treated with Tyverb. It can affect the way the

medicine works.

Pregnancy and breast-feeding

The effect of Tyverb during pregnancy is not known. You should not use Tyverb if you are pregnant unless your doctor specifically recommends it.

- **If you are pregnant** or planning to become pregnant, **tell your doctor.**
- **Use a reliable method of contraception** to avoid becoming pregnant while you're taking Tyverb and for at least 5 days after the last dose.
- **If you become pregnant** during treatment with Tyverb, **tell your doctor**.

It is not known whether Tyverb passes into breast-milk. Do not breast-feed while taking Tyverb and for at least 5 days after the last dose.

- **If you are breast-feeding** or planning to breast-feed, **tell your doctor**.

Ask your doctor or pharmacist for advice before taking Tyverb if you are unsure**.**

Driving and using machines

You are responsible to decide if you are able to drive a motor vehicle or perform other tasks that require increased concentration. Because of the possible side effects of Tyverb, your ability to drive or operate machines could be affected. These effects are described in section 4, 'Possible side effects'.

Tyverb contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Tyverb

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you're not sure.

Your doctor will decide on the correct dose of Tyverb depending on the type of breast cancer being treated.

If you are prescribed Tyverb in **combination with capecitabine**, the usual dose is **5 Tyverb tablets a day**, as a single dose.

If you are prescribed Tyverb in **combination with trastuzumab**, the usual dose is **4 Tyverb tablets a day**, as a single dose.

If you are prescribed Tyverb in **combination with an aromatase inhibitor**, the usual dose is **6 Tyverb tablets a day**, as a single dose.

Take the prescribed dose every day for as long as your doctor tells you to.

Your doctor will advise you about the dose of your other anti-cancer medicine, and how to take it.

Taking your tablets

- **Swallow the tablets whole with water**, one after the other, at the same time each day.
- **Take Tyverb either at least one hour before or at least one hour after food**. Take Tyverb at the same time in relation to food each day – for example, you could always take your tablet one hour before breakfast.

While you are taking Tyverb

- Depending on the side effects you experience, your doctor may recommend lowering your dose or temporarily stopping your treatment.
- Your doctor will also carry out tests to check your heart and liver function before and during treatment with Tyverb.

If you take too much Tyverb

Contact a doctor or pharmacist immediately. If possible, show them the pack.

If you forget to take Tyverb

Don't take a double dose to make up for a forgotten dose. Just take the next dose at the scheduled time.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

A severe allergic reaction is a rare side effect (may affect up to 1 in 1,000 people) and may develop rapidly.
Symptoms may include:
- skin rash (including itchy, bumpy rash)
- unusual wheezing, or difficulty in breathing
- swollen eyelids, lips or tongue
- pains in muscles or joints
- collapse or blackout.

Tell your doctor immediately if you get any of these symptoms. Don't take any more tablets.

Very common side effects (may affect more than 1 in 10 people):

- diarrhoea (which may make you dehydrated and lead to more severe complications)
  Tell your doctor immediately at the first sign of diarrhoea (loose stool), as it is important that this is treated right away. Also tell your doctor immediately if your diarrhoea worsens. *There is more advice on reducing the risk of diarrhoea at the end of section 4.*

- rash, dry skin, itching
  Tell your doctor if you get a skin rash. *There is more advice on reducing the risk of skin rash at the end of section 4.*

Other very common side effects

- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- tiredness, feeling weak
- indigestion
- constipation
- sore mouth/mouth ulcers
- stomach pain
- trouble sleeping
- back pain

- pain in hands and feet
- joint or back pain
- a skin reaction on the palms of the hands or soles of the feet (including tingling, numbness, pain, swelling or reddening)
- cough, shortness of breath
- headache
- nose bleed
- hot flush
- unusual hair loss or thinning

Tell your doctor if any of these side effects get severe or troublesome.

Common side effects (may affect up to 1 in 10 people):

- an effect on how your heart works

In most cases, the effect on your heart will not have any symptoms. If you do experience symptoms associated with this side effect, these are likely to include an irregular heartbeat and shortness of breath.

- liver problems, which may cause itching, yellow eyes or skin (*jaundice*), or dark urine or pain or discomfort in the right upper area of the stomach
- nail disorders – such as a tender infection and swelling of the cuticles
- skin fissures (deep cracks on the skin or chapped skin)

Tell your doctor if you get any of these symptoms.

Uncommon side effects (may affect up to 1 in 100 people):

- treatment-induced lung inflammation, which may cause shortness of breath or cough
  Tell your doctor immediately if you get either of these symptoms.

Other uncommon side effects include:
- blood tests results that show changes in liver function (usually mild and temporary)

Rare side effects (may affect up to 1 in 1,000 people):

- severe allergic reactions (*see the beginning of section 4*)

The frequency of some side effects is not known (it cannot be estimated from the available data):
- irregular heart-beat (change in the electrical activity of the heart)
- severe skin reaction that might include: rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever or any combination of these
- pulmonary arterial hypertension (increased blood pressure in the arteries (blood vessels) of the lungs)

If you get other side effects

Tell your doctor or pharmacist if you notice any side effects not listed in this leaflet.

Reducing the risk of diarrhoea and skin rash

Tyverb can cause severe diarrhoea

If you suffer from diarrhoea while taking Tyverb:

- drink plenty of fluids (8 to 10 glasses a day), such as water, sports drinks or other clear liquids
- eat low-fat, high protein foods instead of fatty or spicy foods
- eat cooked vegetables instead of raw vegetables and remove the skin from fruits before eating
- avoid milk and milk products (including ice cream)
- avoid herbal supplements (some may cause diarrhoea).

Tell your doctor if your diarrhoea continues.

Tyverb can cause skin rash

Your doctor will check your skin before and during treatment.
To care for sensitive skin:

- wash with a soap-free cleanser
- use fragrance free, hypoallergenic beauty products
- use sunscreen (Sun Protection Factor [SPF] 30 or higher).

Tell your doctor if you get a skin rash.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tyverb

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister or bottle and the carton.

Do not store above 30ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Tyverb contains

- The active substance in Tyverb is lapatinib. Each film-coated tablet contains lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib.
- The other ingredients are: microcrystalline cellulose, povidone (K30), sodium starch glycolate (Type A), magnesium stearate, hypromellose, titanium dioxide (E171), macrogol (400), polysorbate 80, iron oxide yellow (E172), and iron oxide red (E172).

What Tyverb looks like and contents of the pack

Tyverb film-coated tablets are oval, biconvex, yellow film-coated, with ‘GS XJG’ marked on one side.

Tyverb is supplied in either blisters packs or bottles:

Blister packs
Each pack of Tyverb contains 70 or 84 tablets in aluminium foil blisters of 10 or 12 tablets each. Each foil has a perforation down the middle and can be divided into two blisters with 5 or 6 tablets in each, depending on the pack size.

Tyverb is also available in multipacks containing 140 tablets that comprise 2 packs, each containing 70 tablets.

Bottles
Tyverb is also available in plastic bottles containing 70, 84, 105 or 140 tablets.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.