The recommended daily dose of erlotinib tablets for NSCLC is 150 mg taken on an empty stomach, i.e.,

- Erlotinib tablets are not recommended for use in combination with platinum-based chemotherapy

Limitations of use:

- Renal failure: Monitor renal function and toxicity. (5.2)

8.2 Lactation

5.8 Ocular Disorders

5.6 Cerebrovascular Accident

NSCLC

- Cigarette smoking and CYP1A2 inducers concentrations. Avoid concomitant use. If not CYP1A2 inhibitor increase erlotinib plasma concentrations. Avoid concomitant use. If not

Gemcitabine

Administered Concurrently with in Maintenance Treatment of Patients

5.5 Bullous and Exfoliative Skin Disorders

The most frequent (≥ 30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, headache, nausea, vomiting, oral candidiasis, mucositis, and hemoptysis. Less frequent (10% to 29%) adverse reactions included rash, asthenia, cough, dyspnea, nausea, vomiting, and hemoptysis. The pooled incidence of bullous and exfoliative skin disorders in the plus gemcitabine arm and 0% in the control arm.

5.9 Hemorrhage in Patients Taking Warfarin

Interaction with coumarin-derived anticoagulants, including warfarin, leading to increased International

Erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP2C8 and CYP2C19. CYP3A4 is a major enzyme involved in the metabolism of erlotinib. Erlotinib is a potent inhibitor of CYP3A4 and CYP1A2. Coadministration of erlotinib with drugs that are metabolized by CYP3A4 and CYP1A2 may result in increased plasma concentrations of these drugs, leading to an increased risk of toxicity.

Metabolism

Erlotinib is eliminated with a median half-life of 36.2 hours in patients receiving the single-agent erlotinib 150 mg tablets. The plasma clearance of erlotinib is decreased in patients with hepatic impairment, and the AUC is increased by approximately 4-fold in patients with mild or moderate hepatic impairment and by approximately 7-fold in patients with severe hepatic impairment. The AUC is increased by approximately 3-fold in patients with moderate renal impairment. In patients with severe renal impairment, the AUC is increased by approximately 6-fold.

Absorption

Erlotinib is about 60% absorbed after oral administration. Peak plasma levels occur 4 hours after dosing. The absorption of erlotinib is not significantly affected by food or by the coadministration of a proton pump inhibitor. The clearance of erlotinib is decreased in patients with hepatic impairment, and the AUC is increased by approximately 4-fold in patients with mild or moderate hepatic impairment and by approximately 7-fold in patients with severe hepatic impairment. The AUC is increased by approximately 3-fold in patients with moderate renal impairment. In patients with severe renal impairment, the AUC is increased by approximately 6-fold.

Dose tin, the risk of adverse reactions associated with erlotinib treatment increases with increasing levels of hepatic impairment. The risk of adverse reactions associated with erlotinib treatment increases with increasing levels of renal impairment. The risk of adverse reactions associated with erlotinib treatment increases with increasing levels of renal impairment. The risk of adverse reactions associated with erlotinib treatment increases with increasing levels of renal impairment.

12.3 Pharmacokinetics

Erlotinib is a potent inhibitor of CYP3A4 and CYP1A2. Coadministration of erlotinib with drugs that are metabolized by CYP3A4 and CYP1A2 may result in increased plasma concentrations of these drugs, leading to an increased risk of toxicity. Coadministration of erlotinib with drugs that are metabolized by CYP3A4 and CYP1A2 may result in increased plasma concentrations of these drugs, leading to an increased risk of toxicity.

Based on animal data and its mechanism of action, erlotinib can cause fetal harm when administered to pregnant women. In animal reproduction studies, erlotinib did not impair fertility in either male or female rats. In female rats treated with doses of 3, 10, and 30 mg/kg/day, the no-observed-effect level was 10 mg/kg/day. In male rats treated with doses of 3, 10, and 30 mg/kg/day, the no-observed-effect level was 30 mg/kg/day.

6.2 Post-Marketing Experience

The most frequent (≥ 30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, headache, nausea, vomiting, oral candidiasis, mucositis, and hemoptysis. Less frequent (10% to 29%) adverse reactions included rash, asthenia, cough, dyspnea, nausea, vomiting, and hemoptysis. The pooled incidence of bullous and exfoliative skin disorders in the plus gemcitabine arm and 0% in the control arm.

In a study of 246 patients with advanced non-small cell lung cancer (NSCLC), the median overall survival was 336 days in the erlotinib arm and 249 days in the placebo arm. The median time to progression in the erlotinib arm was 3.5 months and in the placebo arm was 1.9 months. The median time to onset of diarrhea was 12 days. The most frequent (≥ 30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, headache, nausea, vomiting, oral candidiasis, mucositis, and hemoptysis. Less frequent (10% to 29%) adverse reactions included rash, asthenia, cough, dyspnea, nausea, vomiting, and hemoptysis. The pooled incidence of bullous and exfoliative skin disorders in the plus gemcitabine arm and 0% in the control arm.

In a randomized, double-blind, placebo-controlled trial of 138 patients with advanced NSCLC who had not received prior chemotherapy, the median survival time was 6.8 months in the erlotinib arm and 4.9 months in the placebo arm. The median time to progression in the erlotinib arm was 3.5 months and in the placebo arm was 2.9 months. The median time to onset of diarrhea was 14 days. The most frequent (≥ 30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, headache, nausea, vomiting, oral candidiasis, mucositis, and hemoptysis. Less frequent (10% to 29%) adverse reactions included rash, asthenia, cough, dyspnea, nausea, vomiting, and hemoptysis. The pooled incidence of bullous and exfoliative skin disorders in the plus gemcitabine arm and 0% in the control arm.

In a Phase II trial of 24 patients with advanced NSCLC who had not received prior chemotherapy, the median survival time was 10.2 months in the erlotinib arm and 6.4 months in the placebo arm. The median time to progression in the erlotinib arm was 3.8 months and in the placebo arm was 2.3 months. The median time to onset of diarrhea was 15 days. The most frequent (≥ 30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, headache, nausea, vomiting, oral candidiasis, mucositis, and hemoptysis. Less frequent (10% to 29%) adverse reactions included rash, asthenia, cough, dyspnea, nausea, vomiting, and hemoptysis. The pooled incidence of bullous and exfoliative skin disorders in the plus gemcitabine arm and 0% in the control arm.

In a Phase II trial of 16 patients with advanced NSCLC who had not received prior chemotherapy, the median survival time was 10.2 months in the erlotinib arm and 6.4 months in the placebo arm. The median time to progression in the erlotinib arm was 3.8 months and in the placebo arm was 2.3 months. The median time to onset of diarrhea was 15 days. The most frequent (≥ 30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, headache, nausea, vomiting, oral candidiasis, mucositis, and hemoptysis. Less frequent (10% to 29%) adverse reactions included rash, asthenia, cough, dyspnea, nausea, vomiting, and hemoptysis. The pooled incidence of bullous and exfoliative skin disorders in the plus gemcitabine arm and 0% in the control arm.

In a randomized, double-blind, placebo-controlled trial of 188 patients with advanced NSCLC who had not received prior chemotherapy, the median survival time was 6.8 months in the erlotinib arm and 4.9 months in the placebo arm. The median time to progression in the erlotinib arm was 3.5 months and in the placebo arm was 2.9 months. The median time to onset of diarrhea was 14 days. The most frequent (≥ 30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, headache, nausea, vomiting, oral candidiasis, mucositis, and hemoptysis. Less frequent (10% to 29%) adverse reactions included rash, asthenia, cough, dyspnea, nausea, vomiting, and hemoptysis. The pooled incidence of bullous and exfoliative skin disorders in the plus gemcitabine arm and 0% in the control arm.

In a randomized, double-blind, placebo-controlled trial of 138 patients with advanced NSCLC who had not received prior chemotherapy, the median survival time was 6.8 months in the erlotinib arm and 4.9 months in the placebo arm. The median time to progression in the erlotinib arm was 3.5 months and in the placebo arm was 2.9 months. The median time to onset of diarrhea was 14 days. The most frequent (≥ 30%) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea, headache, nausea, vomiting, oral candidiasis, mucositis, and hemoptysis. Less frequent (10% to 29%) adverse reactions included rash, asthenia, cough, dyspnea, nausea, vomiting, and hemoptysis. The pooled incidence of bullous and exfoliative skin disorders in the plus gemcitabine arm and 0% in the control arm.
The efficacy and safety of single-agent erlotinib was assessed in Study 4, a randomized, double blind, placebo controlled trial, which enrolled 882 patients with unresectable or metastatic pancreatic cancer. Patients were randomized 2:1 to receive erlotinib 150 mg or placebo (44%). The median time from initial diagnosis to randomization was approximately 5 months (range 0.1 to 31 months) in the 100 mg cohort and 24 patients in the 150 mg cohort) and 284 patients were randomized to receive erlotinib 150 mg or placebo (44%).

Duration of response was also examined. The study was conducted in the United States, Canada, and other countries. The median number of cycles received was 6 cycles (range 1 to 22 cycles).

Results from two, multicenter, placebo-controlled, randomized, trials in over 1000 patients conducted in the United States, Canada, and other countries were reported. Median overall survival (OS) was 12.0 months (95% CI: 10.6, 13.9) in the erlotinib 100 mg arm and 11.0 months (95% CI: 9.9, 12.1) in the erlotinib 150 mg arm, yielding a hazard ratio of 0.81 (95% CI: 0.70, 0.95) (p < 0.001)

Figure 2 depicts the Kaplan-Meier Curves for Overall Survival (ITT Population).

Figure 3 depicts the Kaplan-Meier curves for overall survival.

### Objective Response Rate

- **Erlotinib 150 mg**: 17% (95% CI: 0.13, 0.21)
- **Erlotinib 100 mg**: 16% (95% CI: 0.12, 0.20)
- **Placebo**: 14% (95% CI: 0.10, 0.19)

### Progression-Free Survival (PFS)

- **Erlotinib 150 mg**: 6.7 months (95% CI: 5.5, 7.8)
- **Erlotinib 100 mg**: 6.0 months (95% CI: 5.1, 7.1)
- **Placebo**: 4.7 months (95% CI: 4.1, 6.3)

### Median OS in Months (95% CI)

- **Erlotinib 150 mg**: 12.0 (10.6, 13.9)
- **Erlotinib 100 mg**: 11.0 (9.9, 12.1)
- **Placebo**: 4.7 (4.1, 6.3)

### Hazard Ratio (95% CI)

- 0.81 (0.70, 0.95)

### p-value (stratified log-rank test)

- *p < 0.0001*

### Baseline Demographics

- **Gender**: Male (74%), Female (26%)
- **Age**: < 65 years (66%), > 65 years (34%)
- **Race**: White (84%), Black (4%), Other (12%)
- **ECOG PS**: 0 (13%), 1 (53%), 2 (25%)
- **Histology**: Adenocarcinoma (50%), Squamous (30%), Undifferentiated (12%), Other (27%)
- **Smoking Status**: Never smoker (17%), Former smoker (55%), Current smoker (27%)
- **Histologic Subtypes**: Bronchioalveolar (45%), Squamous (40%), Large cell (5%)

### Tumor Characteristics

- **Histology**: Adenocarcinoma (50%), Squamous (30%), Undifferentiated (12%), Other (27%)
- **Histologic Subtypes**: Bronchioalveolar (45%), Squamous (40%), Large cell (5%)
- **EGFR Status**: Positive (70%), Negative (30%)
- **Histologic Subtypes**: Adenocarcinoma (50%), Squamous (30%), Undifferentiated (12%)
- **Histologic Subtypes**: Bronchioalveolar (45%), Squamous (40%), Large cell (5%)

### Side Effects

- **Skin Toxicity**: Rash (93%), Skin dryness (27%), Skin irritation (27%), Skin ulceration (5%)
- **Respiratory Toxicity**: Interstitial lung disease (25%)

### Administration

- **Route**: Oral
- **Dose**: Erlotinib (100 mg, 150 mg)

### Interaction

- **Additive**: Erlotinib may increase the risk of cerebrovascular accident and should be avoided with warfarin (Coumadin), other anticoagulants, and cyclosporine.

### Patient Counseling

- **Skin Toxicity**: Rash, dry skin, and irritation.
- **Respiratory Toxicity**: Interstitial lung disease.
- **Other**: Diabetic retinopathy, keratitis, ophthalmologic changes, noninfectious pneumonia, papillary thyroid cancer, and new or worsening skin conditions.

### Other Information

- **Package Insert**: Available at [www.teva.com](http://www.teva.com).
- **Prescribing Information**: Available at [www.teva.com](http://www.teva.com).
- **Adverse Events**: Reported at [www.adverseevents.com](http://www.adverseevents.com).

For further information please call 1-888-838-2872.