เอกสารกำกับยาภาษาอังกฤษ

1. Product Name

ZYCEVA 100, ZYCEVA 150

2. Name and Strength of Active Ingredient(s)

ZYCEVA 100 contains Erlotinib hydrochloride 109.3 mg equivalent to Erlotinib 100 mg

ZYCEVA 150 contains Erlotinib Hydrochloride 163.9 mg equivalent to Erlotinib 150 mg

3. Product Description

ZYCEVA 100: White to off-white, round, film-coated tablets, debossed with‘914’ on one side and plain on other side

ZYCEVA 150: White to off-white, round, film-coated tablets, debossed with ‘915’ on one side and plain on other side

List of Excipients: Lactose Monohydrate, Microcrystalline cellulose 101, Microcrystalline cellulose 102, Sodium lauryl sulfate, Crospovidone (Type-A), Crospovidone (Type-B), Hypromellose-6 CPS-2910, Colloidal Silicon Dioxide, Magnesium Stearate and Opadry White

4. Pharmacodynamics/Pharmacokinetics

Mechanism of action

Reversibly inhibits overall epidermal growth factor receptor (HER1/EGFR)-tyrosine kinase activity. Intracellular phosphorylation is inhibited which prevents further downstream signaling, resulting in cell death. Erlotinib has higher binding affinity for EGFR exon 19 deletion or exon 21L85R mutations than for the wild type receptor (Drug Facts and Comparisons 2017 p. 4234 attached p. 7, Drug Information Handbook 2019 p. 839 attached p. 14)

Absorption

- Absorption: 60% on an empty stomach; almost 100% on a full stomach (Drug Facts and Comparisons 2017 p. 4234 attached p. 7)
- Bioavailability: Almost 100% when given with food; 60% without food (Drug Facts and Comparisons 2017 p. 4234 attached p. 7)
- Time to peak, plasma: 4 hours (Drug Facts and Comparisons 2017 p. 4234 attached p. 7, Drug Information Handbook 2019 p. 839 attached p. 14)

Distribution

- 232 L (Drug Facts and Comparisons 2017 p. 4234 attached p. 7, Drug Information Handbook 2019 p. 839 attached p. 14)
- Protein binding: Approximately 93% to albumin and alpha$_1$-acid glycoprotein (Drug Facts and Comparisons 2017 p. 4234 attached p. 7, Drug Information Handbook 2019 p. 839 attached p. 14)

Metabolism

- Hepatic, via CYP3A4 (major), CYP1A1 (minor), CYP1A2 (minor), and CYP1C (minor) (Drug Facts and Comparisons 2017 p. 4234 attached p. 7, Drug Information Handbook 2019 p. 839 attached p. 14)

Excretion

- Primarily as metabolites (Drug Facts and Comparisons 2017 p. 4234 attached p. 7, Drug Information Handbook 2019 p. 839 attached p. 14)
- Feces (83%; 1% as unchanged drug) (Drug Facts and Comparisons 2017 p. 4234 attached p. 7, Drug Information Handbook 2019 p. 839 attached p. 14)
- Urine (8%; <1% as unchanged drug) (Drug Facts and Comparisons 2017 p. 4234 attached p. 7, Drug Information Handbook 2019 p. 839 attached p. 14)
- Half-life elimination: 36.2 hours (Drug Information Handbook 2019 p. 839 attached p. 14, MICROMEDEX® [Database on the internet] 2020 p. 9 attached p. 24)
- Total body clearance: Cancer patients, 5.3 L/hours; cigarette smokers, 24% higher rate of clearance (MICROMEDEX® [Database on the internet] 2020 p. 9 attached p. 24)

5. Indication

Non-small cell lung cancer(NSCLC)

First-line treatment of metastatic non-small cell lung cancer in tumors with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an approved test (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

Treatment of locally advanced or metastatic non-small cell lung cancer after failure of at least 1 prior chemotherapy regimen (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

Maintenance treatment of locally advance or metastatic non-small cell lung cancer when disease has not progressed after 4 cycles of platinum-based first-line chemotherapy (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

Pancreatic cancer

First-line treatment of locally advanced, unreselectable or metastatic pancreatic cancer (in combination with Gemcitabine). (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

6. Recommended dose

General dosing considerations

Select patients for the first-line treatment of metastatic non-small cell lung cancer based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor specimens. Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/CcompanionDiagnostics.(Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

Dosage reduction may be required for patients with hepatic impairment (see hepatic function impairment). (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

Adult

Non-small cell lung cancer (NSCLC): 150 mg daily (Drug Facts and Comparisons 2017 p. 4233 attached p.)

Pancreatic cancer: 100 mg daily (in combination with Gemcitabine) (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

Hepatic function impairment

Hepatic impairment at treatment initiation:

Total bilirubin >ULN or Child-Pugh classes A, B, and C: Use with caution and monitor closely during treatment. (Drug Information Handbook 2019 p. 839 attached p. 14)

Total bilirubin >3 times ULN: Use extreme caution. (Drug Information Handbook 2019 p. 839 attached p. 14)

The following adjustments have also been studied: A reduced starting dose (75 mg once daily) has been recommended in patients with hepatic dysfunction (AST ≥3 times ULN or direct bilirubin 1 to 7 mg/dL), with individualized dosage escalation if tolerated; another study determined that pharmacokinetic and safety profiles were similar

between patients with normal hepatic function and moderate hepatic impairment. (Drug Information Handbook 2019 p. 839-840 attached p. 14-15)

Renalfunction impairment

Renal impairment at treatment initiation:

There has not been studied, although <9% of a single dose is excreted in the urine. (Drug Information Handbook 2019 p. 839 attached p. 14)

Adjustment for toxicity

Dermatologic toxicity:

Bullous, blistering, or exfoliative skin toxicity (severe): Discontinue treatment. (Drug Information Handbook 2019 p. 840 attached p. 15)

Severe rash (unresponsive to medical management): Withhold treatment; may reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤grade 1. (Drug Information Handbook 2019 p. 840 attached p. 15)

Gastrointestinal toxicity:

Diarrhea: Manage with Loperamide; in persistent, severe diarrhea (unresponsive to Loperamide) or dehydration due to diarrhea, withhold treatment; may reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤grade 1. (Drug Information Handbook 2019 p. 840 attached p. 15)

Gastrointestinal perforation: Discontinue treatment. (Drug Information Handbook 2019 p. 840 attached p. 15)

Ocular toxicities:

Acute or worsening ocular toxicities (eg. eye pain): Interrupt and consider discontinuing treatment. If therapy is resumed, reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤grade 1. (Drug Information Handbook 2019 p. 840 attached p. 15)

Corneal perforation or severe ulceration: Discontinue treatment. (Drug Information Handbook 2019 p. 840 attached p. 15)

Keratitis (grade 3 or 4 or grade 2 persisting >2 weeks): Withhold treatment; may reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤grade 1. (Drug Information Handbook 2019 p. 840 attached p. 15)

Pulmonary symptoms:

Acute onset (or worsening) of pulmonary symptoms (eg. Dyspnea, cough, fever): Withhold treatment while evaluating for drug-induced interstitial lung disease; if

resuming treatment, reinitiate with 50 mg dose reduction after symptoms resolve to grade 1 or lower. Discontinue permanently with development of interstitial lung disease. (Drug Information Handbook 2019 p. 840 attached p. 15)

Hepatotoxicity:

Patients with normal hepatic function at baseline: If total bilirubin >3 times ULN and/or transaminases >5 times ULN: Interrupt therapy and consider discontinuing. If treatment is resumed, reinitiate with a 50 mg dose reduction after bilirubin and transaminases return to baseline. (Drug Information Handbook 2019 p. 840 attached p. 15)

Patients with baseline hepatic impairment or biliary obstruction: If bilirubin doubles or transaminases triple over baseline: Interrupt therapy and consider discontinuing. If treatment is resumed, reinitiate with a 50 mg dose reduction after bilirubin and transaminases return to baseline. (Drug Information Handbook 2019 p. 840 attached p. 15)

Severe hepatotoxicity that does not significantly improve or resolve within 3 weeks: Discontinue treatment. (Drug Information Handbook 2019 p. 840 attached p. 15)

Renal toxicity:

Grade 3/4 renal toxicity: Withhold treatment and consider discontinuing. If treatment is resumed, reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤ grade 1. (Drug Information Handbook 2019 p. 839 attached p. 14)

Renal failure associated with hepatorenal syndrome or due to dehydration: Withhold treatment until renal toxicity is resolved. If treatment is resumed, reinitiate with a 50 mg dose reduction after toxicity has resolved. (Drug Information Handbook 2019 p. 839 attached p. 14)

<u>Concomitant therapy</u>

CYP3A4 inhibitors:

Avoid concurrent use if possible.Reduce Erlotinib dose by 50 mg decrements if severe adverse reactions occur with concomitant use of strong cytochrome P450 (CYP-450) 3A4 inhibitors (eg, Atazanavir, Clarithromycin, Grapefruit juice, Grapefruit, Indinavir, Itraconazole, Ketoconazole, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Voriconazole) or an inhibitor of CYP3A4 and CYP1A2 (eg, Ciprofloxacin). (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

CYP3A4 inducers:

Avoid concomitant use, if possible; Increase Erlotinib by 50 mg increments at 2-week intervals to a maximum of 450 mg during concomitant use with CYP3A4 inducers (eg, Rifampin, Rifabutin, Rifapentine, Phenytoin, Carbamazepine, Phenobarbital, St. John's wort). (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

Drugs affecting gastric pH:

Avoid concomitant use with proton pump inhibitors if possible, If treatment with an H_2-receptor antagonist (eg, Ranitidine) is required, give Erlotinib 10 hours after H_2-receptor antagonist dosing and at least 2 hours before the next dose of H_2-receptor antagonist. If antacid is necessary, separate the Erlotinib dose and the antacid dose by several hours. (Drug Facts and Comparisons 2017 p. 4233 attached p. 6)

Dosage adjustment for concomitant smoking

Avoid tobacco smoking if possible. If unavoidable, increase dose at 2-week intervals in 50 mg increments to a maximum dose 300 mg (with careful monitoring); immediately reduce Erlotinib dose to recommended starting dose (based on indication) upon smoking cessation. (Drug Information Handbook 2019 p. 839 attached p. 14)

Duration of therapy

Continue treatment until disease progression or unacceptable toxicity occurs. (Drug Facts and Comparisons 2017 p. 4234 attached p. 7)

7. Mode of administration

- Administer on an empty stomach, 1 hour before or 2 hours after food. (Drug Information Handbook 2019 p. 840 attached p. 15, Drug Facts and Comparisons 2017 p. 4234 attached p. 7, MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)
- For patients unable to swallow whole, tablets may be dissolved in 100 mL water and administered orally or via feeding tube (silicone-based); to ensure full dose is received, rinse container with 40 mL water, administer residue and repeat rinse; administer immediately after preparation. If necessary, an oral suspension may be prepared. (Drug Information Handbook 2019 p. 840 attached p. 15)
- Use appropriate precautions for handling and disposal (NIOSH Group 1 Antineoplastics) (Drug Facts and Comparisons 2017 p. 4234 attached p. 7)
- NIOSH: The use of single gloves by anyone handling intact tablets or administeringfrom a unit-dose package is recommended. In the preparation of

tablets, including cutting, crushing, or manipulating,or handling of uncoated tablets, use double gloves and a protective gown. Prepare in aventilated control device, if possible. Use respiratory protection if not prepared in a controldevice. During administration, wear single gloves, and wear eye/face protection if theformulation is hard to swallow or if the patient may resist, vomit, or spit up. (MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)

8. Contraindication

- Hypersensitivity to Erlotinib or any of the excipients listed in topic 3. (MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)

9. Warnings and precautions

- Cardiovascular: Myocardial infarction/ischemia (including fatality) has been reported; riskincreased in patients with pancreatic cancer. (MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)
- Dermatologic: Bullous, blistering, and exfoliative skin reactions have been reported andincluded possible Stevens-Johnson syndrome/toxic epidermal necrolysis; discontinue treatmentif such severe reactions occur. (MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)
- Gastrointestinal: Gastrointestinal (GI) perforation, including fatal cases, may occur. Patientswith peptic ulceration or diverticular disease and those receiving concomitant anti-angiogenicagents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy may have increased risk;permanently discontinue if a GI perforation occurs. (MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)
- Hematologic: Microangiopathic hemolytic anemia with thrombocytopenia may occur; riskincreased in patients with pancreatic cancer. (MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)
- Hepatic: Hepatotoxicity, including hepatic failure and hepatorenal syndrome, with fatalities, hasbeen reported, even in those with normal hepatic function. Risk increased with baseline hepaticimpairment; monitoring recommended. Therapy interruption or discontinuation may be required. (MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)

- Neurologic: Cerebrovascular accidents, including a fatality, have been reported; risk increased.(MICROMEDEX® [Database on the internet] 2020 p. 3 attached p. 18)
- Ocular: Decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca, andkeratitis have occurred and may increase risk for corneal perforation and ulceration; interrupt ordiscontinue use for acute symptoms, persistent severe keratitis, or eye pain.(MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Renal: Renal insufficiency, hepatorenal syndrome, and acute renal failure (including fatalities)have been reported. Risk may be increased in patients with hepatic impairment and severedehydration. Monitoring recommended; therapy interruption and discontinuation may berequired. (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Respiratory: Cases of serious interstitial lung disease (ILD), including fatal cases, haveoccurred. In the event of acute onset of new or progressive, unexplained pulmonary symptoms(eg, dyspnea, cough, fever), withhold Erlotinib during diagnostic evaluation; discontinue therapyif ILD confirmed. (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)

10. Interactions with other medicaments

Metabolism/Transport effects substrate of CYP1A2 (minor), CYP3A4 (major)

Note: Assignment of major/minor substrate status based on clinically relevant druginteraction potential (Drug Information Handbook 2019 p. 839 attached p. 14)

Avoid concomitant use

Avoid concomitant use of Erlotinib with any of the following:

Conivaptan; Fosphenytoin-Phenytoin; Fusidicacid (systemic); Idelalisib; Proton pump inhibitors (Drug Information Handbook 2019 p. 839 attached p. 14)

Increased effect/toxicity

Erlotinib may increase the levels/effects of:

Fosphenytoin-Phenytoin; Warfarin (Drug Information Handbook 2019 p. 839 attached p. 14)

The levels/effects of Erlotinib may be increased by:

Aprepitant; Ceritinib; Ciprofloxacin (systemic); Conivaptan; CYP3A4 inhibitors (moderate); CYP3A4 inhibitors (strong); Duvelisib; Fluvoxamine; Fosaprepitant;

Fosnetupitant; Fusidicacid (systemic); Grapefruit juice; Idelalisib; Larotrectinib; Mifepristone; Netupitant; Palbociblib; Simeprevir; Stiripentol (Drug Information Handbook 2019 p. 839 attached p. 14)

Decreased effect

The levels/effects of Erlotinib may be decreased by:

Antacids; Bosentan; CYP3A4inducers (moderate); CYP3A4 Inducers (strong); Dabrafenib; Deferasirox; Enzalutamide; Fosphenytoin-Phenytoin; Histamine H_2receptor antagonists; Ivosidenib; Leflunomide; Lorlatinib; Mitotane; Pitolisant; Proton pump inhibitors; Rifabutin; Rifapentine; Sarilumab; Siltuximab; St John's Wort; Teriflunomide; Tobacco (smoked); Tocilizumab (Drug Information Handbook 2019 p. 839 attached p. 14)

11. Pregnancy and lactation

- Pregnancy category D. Adverse events were observed in animal reproduction studies. Based on the mechanism of action, may cause fetal harm if administered in pregnancy. Women of reproductive potential should be advised to avoid pregnancy; highly effective contraception is recommended during treatment and for at least 2 weeks after treatment has been completed. (Drug Facts and Comparisons 2017 p. 4234 attached p. 7)
- Lactation: It is not known if Erlotinib is excreted in breast milk. Due to the potential for serious adverse reactions in the breast-feeding infant, the decision to discontinue breast-feeding or discontinue the drug should take into account the benefits of treatment to the mother. (Drug Facts and Comparisons 2017 p. 4234 attached p. 7)

12. Undesirable effects

Common

- Cardiovascular: Edema (37%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Dermatologic: Alopecia (14%), Pruritus (13% to 16%), Rash, any grade (60% to 85%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Endocrine metabolic: Weight decreased (39%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)

- Gastrointestinal: Abdominal pain (11% to 46%), Diarrhea, any grade (20% to 62%), Flatulence (13%), Indigestion (17%), Inflammatory disease of mucous membrane (17% to22%), Loss of appetite (52%), Nausea (33% to 60%), Vomiting (23% to 42%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Hepatic: Hyperbilirubinemia, Increased liver enzymes (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Immunologic: Infectious disease (24% to 39%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Musculoskeletal: Bone pain (25%), Myalgia (21%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Neurologic: Headache (15%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Ophthalmic: Conjunctivitis (12% to 18%), Keratoconjunctivitis sicca (12%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Psychiatric: Anxiety (13%), Depression (19%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Respiratory: Cough (16% to 48%), Dyspnea, any grade (41% to 45%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Other: Fatigue (52%), Fever (36%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)

Serious

- Cardiovascular: Cardiac dysrhythmia, Grade 3 or higher, Myocardial infarction, Syncope,Grade 3 or higher (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Dermatologic: Rash, Grade 3 or 4 (5% to 14%), Stevens-Johnson syndrome, Toxic epidermal necrolysis (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Gastrointestinal: Bowel obstruction, Grade 3 or higher, Diarrhea, Grade 3 or 4 (2% to 5%), Gastrointestinal hemorrhage, Gastrointestinal perforation, Pancreatitis, Grade 3 or higher (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Hematologic: Deep venous thrombosis (3.9%), Microangiopathic hemolytic anemia, withthrombocytopenia (up to 1.4%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)

- Hepatic: Hepatorenal syndrome, Liver failure (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Neurologic: Cerebrovascular accident (2.5%) (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Ophthalmic: Corneal ulcer, Perforation of cornea (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Renal: Acute renal failure (MICROMEDEX® [Database on the internet] 2020 p. 4 attached p. 19)
- Respiratory: Dyspnea, Grade 3 or 4 (8% to 17%), Interstitial lung disease (MICROMEDEX® [Database on the internet] 2020 p. 5 attached p. 20)

13. Overdose and treatment

Toxicity

A minimum toxic dose has not been established. Single oral doses of 1,000 mg inhealthy adults and weekly oral doses up to 1,600 mg in cancer patients have been well-tolerated. (MICROMEDEX® [Database on the internet] 2020 p. 11 attached p. 26)

Repeat twice-daily doses of Erlotinib 200 mg for only a few days, however, was nottolerated due to severe diarrhea, rash and liver transaminase elevation. Conjunctivitis occurredin a 72-year-old man who inadvertently ingested Erlotinib at a dose of 300 mg once daily for 4days, instead of the prescribed dose of 150 mg once daily. (MICROMEDEX® [Database on the internet] 2020 p. 11 attached p. 26)

Management of overdose

Management of mild to moderate toxicity: Treatment is symptomatic and supportive. Treat persistent nausea and vomiting with several antiemetics of different classes. Administer colony stimulating factors (Filgrastim or Sargramostim) as these patients are at risk for severe neutropenia. (MICROMEDEX® [Database on the internet] 2020 p. 11 attached p. 26)

Management of severe toxicity: Treatment is symptomatic and supportive. Administer colony stimulating factors (Filgrastim or Sargramostim) as these patients are at risk for severe neutropenia. Transfusion of platelets and/or packed red cells may be needed in patients with severe thrombocytopenia, anemia, or hemorrhage. Severe nausea and vomiting may respond to a combination of agents from different drug classes. (MICROMEDEX® [Database on the internet] 2020 p. 11 attached p. 26)

Antidote

None (MICROMEDEX® [Database on the internet] 2020 p. 11 attached p. 26)

14. Storage condition

Stored below 30°C (Part P8 Stability data on the dossier)

15. Dosage form and packaging available

3 blister packs (Alu-Alu) of 10 tablets in 1 carton

16. Name and address of manufacturer/marketing authorization holder

Manufactured by

Cadila Healthcare Limited

Plot No. 1-A/1 & 2, Pharmez (Special Economic Zone), Matoda, Sarkhej-Bavla N.H. No. 8A, Tal-Sanand, Dist-Ahmedabad, 382 213, India

Imported by

Pharmaland (1982) Co., Ltd.

56 SoiSupapong 1, Srinakarin Road, Nongborn, Pravej, Bangkok, 10250

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17. Date of revision of package insert

20 September 2020