**B - Mechanism of Action and Pharmacokinetics**

Gefitinib is an orally active selective inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK), an enzyme that regulates intracellular signalling pathways implicated in the proliferation and survival of cancer cells. EGFR is expressed on the cell surface of many normal cells as well as tumours such as lung, ovarian, breast and head and neck cancer. Activating mutations of EGFR have been described. This class of agents appears to have activity as a single agent in NSCLC, but only erlotinib has shown a survival benefit in randomized phase III studies (NCIC CTG BR.21 – erlotinib). For first-line NSCLC treatment, gefitinib increases progression-free survival as compared to paclitaxel-carboplatin, in patients with mutated EGFR. No difference in overall survival was observed.

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Exposure increases proportionally over the dosing range of 50-250 mg. Steady state is achieved in 7-10 days. Bioavailability 60%. Bioavailability not significantly altered by food, but a significant sustained ↑ in gastric pH (such as with H2 antagonists or PPI) may reduce plasma concentrations of gefitinib.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Gefitinib is extensively distributed throughout body tissues. Cross blood brain barrier? Yes (but low) PPB Yes (90%)</td>
</tr>
</tbody>
</table>
Metabolism

Primarily metabolized in the liver via cytochrome P450 (CYP) 3A4; CYP2D6 is involved in the formation of the major metabolite. Poor CYP2D6 metabolizers achieved 2 times higher mean gefitinib exposure than extensive metabolizers.

<table>
<thead>
<tr>
<th>Active metabolites</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive metabolites</td>
<td>O-desmethyl gefitinib and others</td>
</tr>
</tbody>
</table>

Elimination

Excretion is predominantly via the feces (86%)

<table>
<thead>
<tr>
<th>Urine</th>
<th>&lt;4% of dose</th>
</tr>
</thead>
</table>

Half-life

31 - 41 hours (mean terminal t ½).

C - Indications and Status

Health Canada Approvals:

- First-line treatment of patients with locally advanced (incurable) or metastatic non-small cell lung cancer, who have activating mutations of the EGFR tyrosine kinase.

Other Uses:

- Head and neck cancer

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following table contains adverse effects reported from the IPASS trial for the 250mg daily dose.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT* (%)</th>
<th>ONSET**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Arterial thromboembolism</td>
<td>E</td>
</tr>
</tbody>
</table>

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### Gefitinib

**Dermatological**
- Abnormal eyelash growth
  - Alopecia (11%)
  - Cutaneous vasculitis (rare)
- Other - Skin fissures
- Paronychia (14%)
- Rash (52%) (may be severe)

**Gastrointestinal**
- Anorexia (19%)
  - Constipation (12%)
  - Diarrhea (47%) (may be severe)
  - GI perforation (rare)
- Mucositis (13%)
- Nausea, vomiting (17%)

**General**
- Fatigue (14%)

**Hematological**
- Hemorrhage (4%) (may be severe)
- Myelosuppression (7%) (severe < 2%)

**Hepatobiliary**
- ↑ LFTs (11%) (may be severe)
- Pancreatitis (rare)

**Hypersensitivity**
- Hypersensitivity (rare)

**Musculoskeletal**
- Musculoskeletal pain (8%)

**Nervous System**
- Insomnia (15%)
- Neuropathy (4%)

**Ophthalmic**
- Blepharitis (7%)
- Conjunctivitis (7%)
- Dry eye (7%), keratitis (<1%, may be severe)

**Renal**
- Creatinine increased (2%) (may be severe)

**Respiratory**
- Cough, dyspnea (9%)
- Interstitial lung disease (1%)

---

* "Incidence" may refer to an absolute value or the higher value from a reported range.

"Rare" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = immediate (onset in hours to days)  
E = early (days to weeks)  
D = delayed (weeks to months)  
L = late (months to years)

Gefitinib was generally well-tolerated, with the most commonly reported effects being gastrointestinal (diarrhea, nausea and vomiting) and skin changes (rash, acne, dry skin, and
pruritus).

**Skin reactions** (acneiform rash on face, scalp or chest) are common and usually mild to moderate, but may be severe. They usually appear by day 10 to 14 of treatment, may diminish with continued treatment, and are reversible when drug is withdrawn. In some patients the rash may be itchy or painful, cosmetically worrisome or associated with paronychiae, and usually be managed with a brief interruption of therapy.

**Diarrhea** is another frequently occurring adverse event; 1% of patients have grade 3 or 4 diarrhea, which may be associated with dehydration and should be managed appropriately. Problematic symptoms can also be managed by providing a brief therapy interruption.

**Renal failure** has been observed and is secondary to dehydration due to diarrhea, nausea/vomiting, anorexia, concurrent infections, or concurrent medications (e.g. chemotherapy).

**Interstitial Lung Disease** has been reported in 1% of patients receiving gefitinib, and may be fatal in up to a third of the cases. The reported incidence appears higher in Japan. The incidence may increase in patients with pre-existing ILD, a recent diagnosis of NSCLC (< 6 months) with poor PS, with concurrent heart disease, who are ≥ 55 years or are current smokers. If patients present with worsening of respiratory symptoms such as dyspnea, cough and fever, gefitinib should be interrupted and prompt investigation initiated.

**Hemorrhages** have been reported in 4% of patients but may be fatal, and usually involve gastrointestinal or respiratory systems. Rare, fatal cases of gastrointestinal perforation have been reported in patients with risk factors such as concomitant NSAIDs or steroids, history of GI ulcer, age, smoking, GI obstruction, advanced bowel disease and bowel metastases at perforation sites.

Corneal erosion is uncommon with gefitinib use and is reversible. Other generally mild **ophthalmic** symptoms such as conjunctivitis, blepharitis, abnormal eyelash growth and dry eye are commonly reported. Recent corneal surgery and contact lens wearing are independent risk factors for ocular toxicity. Patients should be instructed to seek medical attention promptly if any eye symptoms develop.

**E - Dosing**

Use only in patients with known EGFR mutations; clinical characteristics are not sufficient.

**Adults:**

Oral: 250mg once daily with or without food

**Dosage with Toxicity:**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 skin, eye toxicity, poorly tolerated</td>
<td>Hold*, restart at 250mg daily when recovered</td>
</tr>
</tbody>
</table>
diarrhea

Grade 3 skin, eye toxicity, diarrhea, LFTs, dehydration

Hold*, may restart at 250mg daily when recovered

Grade 4 toxicities OR GI perforation OR treatment intolerance despite dose interruption

Discontinue

(Continued on next page)

<table>
<thead>
<tr>
<th>Toxicity (Continued)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratitis</td>
<td>Hold and investigate. Consider discontinuing if ulcerative.</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Hold in the presence of cough/dyspnea/fever and investigate. Discontinue if pneumonitis confirmed.</td>
</tr>
</tbody>
</table>

* up to 14 days for diarrhea and skin toxicity

**Dosage with Hepatic Impairment:**

Increased gefitinib exposure has been reported in patients with moderate and severe hepatic impairment due to cirrhosis. Dose adjustment is not required, but use with caution and monitor closely. Exercise caution in patients with mild to moderate changes in liver function; consider discontinuing gefitinib with severe changes in liver function.

**Dosage with Renal Impairment:**

No adjustment required in mild or moderate renal impairment. No specific recommendations were found for patients with severe renal impairment.

**Dosage in the elderly:**

No adjustment required.

**Dosage in other populations:**

No dose adjustment required based on gender, body weight, or ethnicity.

**Children:**

Safety and efficacy not established. May have increased risk of CNS bleeding.
F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- May be administered with or without food.
- Avoid grapefruit, pomegranate, starfruit, Seville oranges, their juices or products during gefitinib treatment
- Missed dose should be taken as soon as possible, but only if there are at least 12 hours before the next dose is due. Otherwise, skip and take the next dose as scheduled.

G - Special Precautions

Contraindications:

- in patients with severe hypersensitivity to gefitinib or to any of its excipients
- EGFR mutation negative tumours

Other Warnings/Precautions:

- contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- risk of mortality among patients who develop ILD is higher in patients who are smokers, have pre-existing ILD, ≥ 65 years old, or have extensive areas adherent to the pleura.

Other Drug Properties:

- Carcinogenicity: Yes
  Gefitinib has potential phototoxic and contact sensitizing effects.

Pregnancy and Lactation:

- Genotoxicity: No
- Crosses placental barrier: Yes
- Fetotoxicity: Yes
  Women of childbearing potential should be advised to avoid becoming pregnant while receiving gefitinib treatment. Adequate contraception should be used in both sexes during gefitinib treatment and for 6 months after the last dose.
- Fertility effects: Yes
  Female fertility was affected in animals.
- Excretion into breast milk: Yes
  Breastfeeding is not recommended.
### H - Interactions

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John’s Wort, etc)</td>
<td>↓ gefitinib exposure (up to 83%), may ↓ efficacy</td>
<td>↑ metabolism of gefitinib</td>
<td>Caution; avoid co-administering with strong CYP3A4 inducers</td>
</tr>
<tr>
<td>CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)</td>
<td>↑ gefitinib exposure (up to 80%)</td>
<td>↓ metabolism of gefitinib</td>
<td>Caution; avoid co-administering with strong CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Proton pump inhibitors --PPI's (e.g. omeprazole etc.) and other drugs that increase gastric pH</td>
<td>↓ gefitinib exposure, may ↓ efficacy</td>
<td>↑ Gastric pH, reduces absorption</td>
<td>Caution</td>
</tr>
<tr>
<td>Coumadin (warfarin)</td>
<td>↑ anticoagulant effect</td>
<td>Unknown</td>
<td>Caution, monitor INR closely</td>
</tr>
<tr>
<td>Histamine H2-receptor antagonists (e.g. ranitidine, famotidine etc.)</td>
<td>↓ gefitinib exposure (47% by ranitidine), may ↓ efficacy</td>
<td>↑ gastric pH, reduces absorption</td>
<td>Caution</td>
</tr>
<tr>
<td>CYP2D6 substrates (e.g. beta-blockers, tramadol, nortriptyline, mirtazapine,</td>
<td>↑ CYP2D6 substrate plasma concentration</td>
<td>gefitinib is a potentially mild inhibitor of CYP2D6 (In vitro)</td>
<td>None (clinically insignificant for metoprolol). Consider dose reduction for CYP2D6 substrates with narrow therapeutic</td>
</tr>
</tbody>
</table>
I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

**Recommended Clinical Monitoring**

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function tests</td>
<td>baseline and routine</td>
</tr>
<tr>
<td>Electrolytes, creatinine and urea, especially in patients at high risk of dehydration</td>
<td>baseline and periodic</td>
</tr>
<tr>
<td>INR in patients on warfarin, especially initially, or when gefitinib is held or discontinued</td>
<td>Baseline and regular</td>
</tr>
<tr>
<td>Clinical assessments and grading of GI, skin, eye and respiratory symptoms</td>
<td>At each visit</td>
</tr>
</tbody>
</table>

Grade toxicity using the current [NCI-CTCAE (Common Terminology Criteria for Adverse Events) version](http://www.cancer.gov/)  

J - Supplementary Public Funding

**Exceptional Access Program** ([EAP Website](http://www.cancer.gov/))

- gefitinib - First-line monotherapy in locally advanced (not amenable to curative therapy) or metastatic NSCLC patients who have activating mutations of EGFR-TK, with specific criteria

K - References


**June 2019** Updated emetic risk category.

Refer to the *New Drug Funding Program* or *Ontario Public Drug Programs* websites for the most up-to-date public funding information.

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