Criteria for Nonformulary Use of Gefitinib (Iressa™)
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VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

1. In June 2005, the FDA issued a Public Health Advisory about new labeling changes and a restricted access distribution program for gefitinib. This was due to the results of a phase III trial that showed no survival benefit when gefitinib was compared to placebo in patients who had failed on one or two prior treatments for non-small cell lung cancer. The Iressa Access Program will be effective September 15, 2005.

There will be no new patients started on gefitinib starting August 1, 2005 except for patients enrolling in IRB approved non-IND investigational protocols as outlined below.

Gefitinib 250mg once a day may be used according to the following criteria:

- Palliative treatment of locally advanced or metastatic non-small cell lung cancer in patients currently receiving and benefiting from gefitinib or patients who have previously received or benefited from gefitinib OR
- Previously enrolled patients or new patients in non-Investigational New Drug (IND) clinical trials approved by an IRB prior to June 17, 2005. OR
- Gefitinib may be available to new patients if AstraZeneca makes it available under an IND.
- Patient understands that the treatment is for palliation only and has signed the Iressa™ Access Program Patient Consent Form for prescriptions continuing after September 15, 2005.
- Prescribing should be limited to 30 days per prescription

Monitor:

- Reassess every 4 weeks during gefitinib therapy for symptom improvement, using the LCS, and for objective response. If disease is not at least stable and symptoms have not improved by at least 2 points on the LCS, then therapy should be discontinued. There is no evidence that increasing the dose will increase the response rate.
- Routine monitoring of AST/ALT because of asymptomatic increases in liver enzymes. Discontinue therapy if increases are severe.
- Routine antiemetics are not necessary, but antiemetics should be available on a prn basis.
- Loperamide is useful if diarrhea is severe.

Exclusions:

- Caution in prescribing to patients with pre-existing interstitial lung disease
- Should not be used in first line therapy and/or in combination with chemotherapy in chemotherapy-naïve patients
- Pregnancy category D: there are no adequate trials of gefitinib in pregnancy

Patient Information:

- Seek immediate medical care with the development of severe or persistent diarrhea, nausea, or vomiting which may lead to dehydration
- Seek immediate medical care for new or worsening pulmonary symptoms: dyspnea, cough, and/or fever
- Seek medical care if new eye irritation or eye pain develops

2. Dosing

The recommended dose is 250mg once a day with or without food. In patients taking inducers of CYP3A4 like rifampin and phenytoin, consider increasing the dose to 500mg once a day in the absence of severe adverse drug reactions.

Dose Adjustments

1. Poorly tolerated **diarrhea** (with or without dehydration): Hold dose for up to 14 days, then reinstate at 250mg per day.
2. **Skin** adverse reactions: Hold dose for up to 14 days, then reinstate at 250mg per day.
3. Acute onset or worsening **pulmonary symptoms** (dyspnea, cough, fever): Hold dose and investigate symptoms. If interstitial lung disease is confirmed, discontinue gefitinib and initiate appropriate therapy.
4. If new **eye symptoms** develop, such as pain, evaluate and manage appropriately including interruption of gefitinib therapy and removal of abnormal eyelashes. Once symptoms resolve, consider restarting gefitinib.
5. If receiving **potent CYP3A4 inducers** (rifampin or phenytoin) consider increasing dose to 500mg per day in the absence of severe adverse reactions.

Drug Interactions:

Inducers of CYP3A4: May decrease plasma levels of gefitinib. Consider increasing dose to 500mg in the absence of adverse effects.

Inhibitors of CYP3A4 (itraconazole and ketoconazole): May increase plasma levels of gefitinib causing increased clinically significant adverse effects. Use concurrently with caution.

Warfarin: Concurrent use may increase INR and/or bleeding events. Patients should be monitored regularly for changes in INR.

Sustained elevations in gastric pH (ranitidine or cimetidine): May decrease gefitinib plasma concentrations and reduce efficacy.

3. Safety

Gefitinib is generally well tolerated. The majority of toxicities in phase II clinical trials were grade 1 or 2 and affected the skin (acneform rash, rash, dry skin, pruritus) and the GI tract (diarrhea, nausea, and vomiting).

Ocular irritation due to aberrant eyelash growth was primarily seen in phase I dose-finding studies.

Interstitial lung disease (ILD) has been diagnosed as interstitial pneumonia, pneumonitis, or alveolitis and often presents as acute dyspnea with or without cough and fever that becomes severe in a short period of time. Two thirds of patients respond to systemic corticosteroid therapy; in one-third the disease in fatal. ILD has also been seen with radiation therapy and chemotherapy.

Hepatotoxicity: Asymptomatic increases in liver enzymes have been observed. If the changes become severe, consider stopping therapy.

4. Trial Summary

To date, there are no randomized controlled trials with gefitinib demonstrating increased survival, improvement of symptoms, or disease response compared to placebo or best supportive care.

Table 3. Registration Trial- Monotherapy in Third-Line Treatment Setting[1]

Outcome	Gefitinib 250mg (N=102)	Gefitinib 500mg (N=114)
Objective Response	11.8%	8.8%
Symptom improvement	43.1%	35.1%
Progression-free survival (median)	59 days	60 days
Median survival	185 days	183 days
Disease Control	42.2%	36%

Entry requirements:

- Patients with locally advanced or metastatic non-small cell lung cancer that had received treatment with at least 2 chemotherapy regimens that were platinum-and docetaxel-based (need not be given concurrently).
- Failures of previous chemotherapy regimens were the result of disease progression during or within 90 days of the last dose of chemotherapy or treatment intolerance.
- Required to have symptomatic disease as evidenced by a score of ≤24 on the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) instrument (a score of 28 on the LCS indicates no symptoms).
- By FDA analysis, 139/216 patients (64%) met the eligibility criterion. Seventy-seven patients were not refractory or intolerant to docetaxel, platinum, or both drugs.

Response:

- 22/216 patients had a partial response for a response rate of 10.2% (95% CI 6.5,15). In 18 patients the response was documented by measurable disease while 4 patients had a PR with non-measurable disease. 61% of patients received 3 or more previous chemotherapy regimens.
- Disease Control-This was determined to not be meaningful because the majority of patients had slow growing tumors (adenocarcinoma histology).
- The majority of patients (72.7%) had an objective response by the third or fourth week; objective responses were seen as late as week 16 of therapy (2 patients).
- Disease related symptom improvement is defined as a sustained 2-point improvement on the LCS for at least 4 weeks without an interim worsening.
- Baseline median LCS score was 16. In patients who had symptom improvement, the median increase in LCS score was 7 points.
- Symptom response correlated with disease response; patients with objective responses had the highest symptom response, followed by stable disease, and then progressive disease. Patients experiencing symptom response also had a longer overall survival.[2]
- FDA believes that symptom improvement without a concurrent, randomized control arm and no prospective plan for collecting data on use of supportive care agents (e.g., oxygen and opiates) is not a reliable measure.
- Patient characteristics associated with variable response rates: women responded better than men (17.5% vs. 5.1%), nonsmokers responded better than current or previous smokers (29.4% vs. 4.6%), and adenocarcinoma histology responded better than other histologies (12.4% vs. 6.7%).

References

[1] Briefing Document NDA 21-399. http://www.fda.gov/ohrms/dockets/ac/02/briefing/3894B1_03_FDA-Medical%20Officer%20Review.pdf
[2] Cella D. Impact of ZD1839 on non-small cell lung cancer-related symptoms as measured by the functional assessment of cancer therapy-lung scale. Sem Onc 2003;30:39-48.

More detailed information regarding gefitinib and references used can be obtained form the gefitinib monograph located on the following web site: http://www.vapbm.org or http://vaww.pbm.med.va.gov

* Lung Cancer Subscale of the FACT-L

Symptoms/Concerns	Not at all	A little bit	Some-what	Quit a bit	Very Much
1. I have been short of breath	0	1	2	3	4
2. I am losing weight	0	1	2	3	4
3. My thinking is clear	0	1	2	3	4
4. I have been coughing	0	1	2	3	4
5. I have a good appetite	0	1	2	3	4
6. I feel tightness in my chest	0	1	2	3	4
7. Breathing is easy for me	0	1	2	3	4

Scoring:

Item Number	Calculation	Item response	= Item score
1.	4 minus	_____	= _____
2.	4 minus	_____	= _____
3.	0 plus	_____	= _____
4.	4 minus	_____	= _____
5.	0 plus	_____	= _____
6.	4 minus	_____	= _____
7.	0 plus	_____	= _____

Sum ITEM SCORES _____ X 7 ÷ (___) = _____
(___) is the number of items answered

Cella DF, et al. Reliability and validity of the Functional Assessment of Cancer Therapy – Lung (FACT-L) quality of life instrument. Lung Cancer 1995;12:199-220.

**Performance Status

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.