GEFITINIB

First-line treatment of locally advanced or metastatic NSCLC, in patients with EGFR-TK mutation
NICE approved July 2010

Drug/Dosage: **Gefitinib** 250mg po once daily as continuous therapy

Administration: Gefitinib is available as a 250mg tablet. The tablet may be swallowed whole with some water, with or without food, at about the same time each day.
For patients who cannot swallow tablets, they may be dispersed as follows:
drop tablet in half a glass of drinking water. Swirl glass occasionally, until the tablet is dispersed (this may take up to 20 minutes). Drink the dispersion immediately after dispersion is complete (i.e. within 60 minutes). Then rinse the glass with half a glass of water, which should also be drunk. Alternatively, the dispersion can be administered through a naso-gastric or gastrostomy tube.

Frequency: Continuous therapy until progression or unacceptable toxicity.
Toxicity review 2 weeks after starting
Full clinical review including CT scan before Cycle 3, to ensure response / stable disease (first 2 cycles are free; dispensing of 3rd cycle incurs a £12,200 charge to cover all further supplies)

Main Toxicities: rash; diarrhoea

Anti- emetics: none usually needed, but some patients may have nausea

Regular:	FBC	monthly
Investigations:	LFTs & U&Es	monthly
	CT scan	at 6 weeks, then every 3 months

Comments: Encourage routine use of a moisturiser at the start of gefitinib treatment to prevent and minimise problems with skin dryness. Aveeno colloidal oatmeal lotion is our recommended moisturiser. This is a moisturiser with anti-inflammatory properties that has been shown in small studies to have good efficacy and no toxicity[1,2]. However, if the patient prefers, they may use a moisturiser of their choice.

Elimination of gefitinib is mainly through hepatic metabolism. Concomitant use of enzyme inducers (e.g. phenytoin, rifampicin, carbamazepine, barbiturates, St John's Wort) with gefitinib should be avoided, as this may increase the risk of therapeutic failure.
Co-administration of gefitinib with enzyme inhibitors (e.g. itraconazole, erythromycin, clarithromycin) should also be avoided. If this is not possible, the patient needs to be closely monitored for gefitinib adverse reactions.

Drugs that reduce gastric acidity reduce the solubility of gefitinib, thereby reducing its absorption. This may reduce the efficacy of gefitinib. There is no formal advice regarding this from the manufacturer, but it is suggested that the concomitant use of PPIs or H_2 antagonists with gefitinib should be avoided where possible.

Although antacids are also predicted to interact, antacid interactions can usually be minimised by separation of administration. e.g. antacids should be taken at least 4 hours before, or 2 hours after, gefitinib.

Reason for Update: 2 week toxicity check added	Approved by Consultant: Dr V Ezhil
Version: 3	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 2	Date: 29.5.14
Prepared by: S Taylor	Checked by: C Tucker

If the patient is taking warfarin, monitor the INR closely when initiating gefitinib. INR elevations and bleeding events have been reported in some patients taking both gefitinib and warfarin.

Dose Modifications

Haematological Toxicity:	Gefitinib is not myelosuppressive. Patients may continue gefitinib during periods of mild myelosuppression. Discuss with doctor if concerned.
Primary Rash:	Ensure moisturiser is being used regularly. The recommended frequency of application for Aveeno colloidal oatmeal lotion is three times daily. Consider using topical hydrocortisone 1% early in patients with mild rash, but use cautiously, especially for severe rash, as efficacy may be limited by inability to penetrate skin. Analgesia may be of benefit. Topical acne medications are **not** recommended. Severe rash may require a short interruption in treatment (up to 14 days) until rash resolved. If severe rash returns when treatment is re-instated, SPC advice is for gefitinib to be discontinued and an alternative treatment considered. However, 250mg po given once every 2 or 3 days has been shown to have no difference in efficacy compared to 250mg daily[3], and may be considered as an option to reduce toxicity.
Infected Rash:	If a pustular component, consider a short course of oral doxycycline or flucloxacillin. Use of topical antibiotics is not encouraged, and needs to be discussed with Microbiology first.
Diarrhoea:	Mild to moderate diarrhoea may be managed with loperamide. In the event of severe diarrhoea, or diarrhoea associated with dehydration, gefitinib therapy should be interrupted for up to 14 days until diarrhoea resolved. If severe diarrhoea returns when treatment is re-instated, SPC advice is for gefitinib to be discontinued and an alternative treatment considered. However, 250mg po given once every 2 or 3 days has been shown to have no difference in efficacy compared to 250mg daily[3], and may be considered as an option to reduce toxicity.
Hepatic Impairment:	Gefitinib is excreted mainly as metabolites via the faeces. Gefitinib plasma concentrations have been shown not to increase in cancer patients with elevated AST, ALP or bilirubin due to liver metastases. However, patients with moderate to severe hepatic impairment (Child Pugh B or C) due to cirrhosis have increased plasma concentrations of gefitinib. These patients should be closely monitored for adverse events.
Renal Impairment:	No dose adjustment is required in patients with CrCl > 20 ml/min. Only limited data are available in patients with creatinine clearance ≤ 20 ml/min and caution is advised in these patients. N.B. So that patients do not have unnecessary delays waiting for their prescription, LFT and serum creatinine results from the previous visit may be used if they are within normal limits and stable.
References:	Mok, T et al; NEJM 2009; 361: 947 – 957 Rash advice adapted from HER1/EGFR Inhibitor Rash Management Forum, 2005 [1]Alexandrescu, D et al; Clinical and Experimental Dermatology 2006; 32: 71 – 74 [2]Talsania, T et al; Clinical and Experimental Dermatology 2008; 33 (1): 108 [3]Inoue, A et al; JCO 2010; 28 (15s): abstract 7571