Afatinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of Epidermal Growth Factor Receptor (EGFR) TKI- naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).	C34	00221a	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Afatinib is administered on a continuous basis once daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Afatinib	40mg daily	PO without food at the same time each day. Tablet may be swallowed whole with water *Food should not be consumed for at least 3 hours before and at least 1 hour after taking this medicinal product.	Continuous
If swallowing of whole tablets is not possible, these can be dispersed in approximately 100 ml of noncarbonated drinking water. No other liquids should be used. The tablet should be dropped into the water without crushing it, and stirred occasionally for up to 15 min until it is broken up into very small particles. The dispersion should be consumed immediately. The glass should be rinsed with approximately 100 ml of water which should also be consumed. The dispersion can also be administered through a gastric tube.			
If a dose is missed it should be taken as soon as the patient remembers except when it is less than 8hrs to the next dose the patient. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose. If a patient vomits within a few hours of taking the drug do not repeat the dose.			

ELIGIBILTY:

- Indications as above
- EGFR activating mutation status as demonstrated by a validated test method

EXCLUSIONS:

- Pregnancy or breast feeding
- Known pre-existing interstitial lung disease (ILD).
- AST or ALT > three times the upper limit of normal (ULN) (if related to liver metastases > five times ULN).
- Creatinine clearance <60ml/min or serum creatinine > 1.5xULN
- Hypersensitivity to afatinib or any of the excipients

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Assessment of LVEF if clinically indicated

Regular tests:

- FBC, renal and *liver profile monthly

*See Adverse Effects/Regimen Specific Complications.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- DOSE ESCALATION: To a maximum of 50mg/day may be considered in patients who tolerate a 40mg/day dose (i.e. absence of diarrhoea, skin rash, stomatitis, and other Grade > 1 adverse reactions) in the first 3 weeks.
- The dose should not be escalated in any patients with a prior dose reduction.
- **The maximum daily dose is 50mg**

Renal and Hepatic Impairment:

Table 1: Dose modification of afatinib in renal and hepatic impairment

Renal Impairment		**Hepatic Impairment**	
eGFR (ml/min/1.73m^2)	**Dose**		**Dose**
15-89	No dose adjustment to starting dose required Monitor patients with severe renal impairment (eGFR 15-29 mL/min/1.73m^2) and adjust afatinib dose if not tolerated.	**Mild Child Pugh Class A**	No dose adjustment to starting dose necessary
		Moderate Child Pugh Class B	
		Severe Child Pugh Class C	Not recommended
<15 or on dialysis	Not recommended		

Management of adverse events:

Table 2: Dose Modification of afatinib for Adverse Events

Adverse reactions	Recommended dose modification
Grade 1 or 2	No interruption[a] or dose adjustment
Grade 2 (prolonged[b] or intolerable) Grade ≥3	Interrupt until reaction has resolved to Grade 0 or 1[a]. Resume with dose reduction by 10mg decrements[c].
Interstitial Lung Disease	Discontinue

[a]In case of diarrhoea, anti-diarrhoeal medicinal products (e.g. loperamide) should be taken immediately and continued for persistent diarrhoea until loose bowel movements cease.

[b]> 48 hours of diarrhoea and/or > 7 days of rash.

[c]If patient cannot tolerate 20 mg/day, permanent discontinuation of afatinib should be considered.
Refer to local policy for prevention and treatment of EGFR-inhibitor adverse skin reactions.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Emollients may be required to prevent dry skin – see local policy.
Counsel patient that they may they experience ocular adverse reactions (conjunctivitis, dry eye, keratitis) which may affect patients ability to drive or use machines.
Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Diarrhoea:** Usually occurs within the first 2 weeks of treatment. Proactive management of diarrhoea including adequate hydration combined with anti-diarrhoea medicinal products especially within the first six weeks of treatment is important and should start at first signs of diarrhoea. Patients with severe diarrhoea may require interruption and dose reduction or discontinuation of therapy with afatinib**.**
- **Skin related adverse events:** In general rash manifests as a mild or moderate erythematous and acneiform rash which may worsen in areas exposed to sun. For patients who are exposed to sun, protective clothing, and use of sun screen is advisable. Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis. Treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions. Refer to local skin policy**.**
- **Female gender, lower body weight and underlying renal impairment:** Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment. This could result in a higher risk of developing adverse reactions in particular diarrhoea, rash/acne and stomatitis. Closer monitoring is recommended in patients with these risk factors.

- **Interstitial Lung Disease (ILD):** If patients experience acute onset and/or worsening of respiratory symptoms such as dyspnoea, cough and fever, treatment should be interrupted and the patient should be promptly investigated. If ILD is confirmed, afatinib should be permanently discontinued and the patient treated appropriately**.**
- **Hepatitis, hepatic failure:** Periodic liver function testing is recommended in patients with pre-existing liver disease. Dose interruption may become necessary in patients who experience worsening of liver function. In patients who develop severe hepatic impairment while taking afatinib, treatment should be discontinued**.**
- **Keratitis:** Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment should be interrupted or discontinued. This medicinal product should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration**.**
- **Cardiac toxicity:** In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered. In patients with an ejection fraction below the institution's lower limit of normal, cardiac consultation as well as treatment interruption or discontinuation should be considered.
- **Gastrointestinal perforations:** Gastrointestinal perforation, including fatalities, has been reported during treatment with afatinib in 0.2% of patients across all randomized controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. In patients who develop gastrointestinal perforation while taking afatinib, treatment should be permanently discontinued.

DRUG INTERACTIONS:

- In vitro studies have demonstrated that afatinib is a substrate for P-gp and Breast Cancer Resistance Protein (BCRP). Strong P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) should be administered using staggered dosing, preferably 6 hours or 12 hours apart from afatinib.
- Strong P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's wort (Hypericum perforatum)) may decrease exposure to afatinib
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Afatinib	L01XE13

REFERENCES:

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5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	20/12/2013	Initial Draft	Dr Linda Coate
2	01/02/2016	Updated Adverse Events/Regimen specific complications	Dr Linda Coate
3	22/02/2018	Updated emetogenic status, dosing in renal and hepatic impairment and adverse effects as per SmPC. Updated with new NCCP regimen template	Prof Maccon Keane
4	26/02/2020	Reviewed. Update of emetogenic potential. adverse events.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.