OSIMERTINIB

For the treatment of adult patients with locally advanced or metastatic EGFR T790M +ve NSCLC

Blueteq registration is required before treatment may start

Drug/Dosage: **Osimertinib** initiate at 80mg po once daily as continuous therapy

Administration: Osimertinib is available as 80mg and 40mg tablets.
The daily dose should be swallowed whole with water, with or without food, at the same time each day. It should not be chewed or crushed.

For patients who cannot swallow tablets, the dose may be dispersed in approx 50ml of noncarbonated drinking water. The tablet should be dropped into the water without crushing it, and stirred until dispersed. The dispersion should be swallowed immediately. The glass should then be rinsed with further water which should also be swallowed.

The dispersion can also be administered through a gastric tube – in this case, use 15ml volume for initial dispersion, plus a 15ml volume for residue rinse.

Frequency: Continuous therapy until progression or unacceptable toxicity.
Toxicity review 2 weeks after starting

Main Toxicities: rash; diarrhoea; myelosuppression; stomatitis; paronychia; interstitial lung disease (ILD) or pneumonitis

Anti- emetics: none usually needed

Regular:	FBC	monthly
Investigations:	LFTs & U&Es	monthly
	QTc	for patients with CHF, electrolyte abnormalities or on other medicines known to prolong QTc, check QTc at baseline, after one month, then as indicated
	CT scan	every 3 months

Comments: Ensure patients still have a supply of loperamide, and encourage patient to use loperamide promptly and pro-actively at the first sign of any diarrhoea.

Encourage routine use of a moisturiser at the start of osimertinib treatment to prevent and minimise problems with skin dryness.

Interactions: Concomitant use of strong CYP3A inducers (e.g. rifampicin, carbamazepine, phenytoin, St. John's wort) should be avoided, as they may increase the risk of therapeutic failure.

However, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib.

Dose Modifications

Haematological Toxicity: If neutrophils < 1.0 x 10^9/l or platelets < 50 x 10^9/l, osimertinib should be interrupted until blood counts have recovered.
If counts recover within 3 weeks of stopping osimertinib, re-start treatment either at 80mg od, or with a reduction to 40mg od.
If blood counts do not recover after 3 weeks, permanently discontinue.

Primary Rash: Ensure moisturiser is being used regularly.
In the event of a Grade 3 rash (papular eruption with or without pruritis, covering 30% of BSA), osimertinib should be interrupted until rash resolved.
Analgesia may be of benefit. Topical acne medications are **not** recommended.
If the rash resolves within 3 weeks, osimertinib may be re-started either at 80mg od, or with a reduction to 40mg od.
If the rash takes longer than 3 weeks to resolve to Grade 0-2, permanently discontinue.

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. Osimertinib therapy may continue.
In the event of an increase of ≥ 7 stools/day over baseline (Grade 3), osimertinib should be interrupted until diarrhoea resolved.
If diarrhoea resolves to Grade 0 – 2 within 3 weeks of stopping osimertinib, re-start treatment either at 80mg od, or with a reduction to 40mg od.
If diarrhoea does not resolve to Grade 0 – 2 after 3 weeks, permanently discontinue.

Mucositis: Grade 3 mucositis was not reported in the pivotal studies.
However, in the event of Grade 3 mucositis, osimertinib should be interrupted until resolved.
If it resolves to Grade 0 – 2 within 3 weeks of stopping osimertinib, re-start treatment either at 80mg od, or with a reduction to 40mg od.
If it does not resolve to Grade 0 – 2 after 3 weeks, permanently discontinue.

QTc interval:

QTc interval	Osimertinib dose modification
>500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc < 481 msec (or recovery to baseline if baseline QTc ≥ 481 msec), then restart at a reduced dose of 40 mg od.
QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue

Pneumonitis/ILD: Permanently discontinue osimertinib

Hepatic Impairment: No dose adjustment is recommended in patients with bilirubin ≤ ULN and AST > ULN, or bilirubin >1.0 - 1.5 x ULN and any AST.
Osimertinib use in patients with moderate or severe hepatic impairment is not recommended, due to lack of safety or efficacy data, and lack of pharmacokinetic data.

Renal Impairment: No start dose adjustment is required in patients with CrCl > 30 ml/min.
Limited data are available in patients with severe renal impairment.
The safety and efficacy has not been established in patients with CrCl <15 mL/min, so caution should be exercised when treating patients with this level of renal impairment.