Osimertinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC)	C34	00353a	CDS 01/07/2020

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.

Osimertinib is administered once daily until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Osimertinib	80mg	PO[a]	N/A	Continuous
The tablet should be swallowed whole with water and it should not be crushed, split or chewed.					
[a]If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50mL of noncarbonated water. It should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added					
If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15mL for the initial dispersion and 15mL for the residue rinses. The resulting 30mL of liquid should be administered as per the naso-gastric tube manufacturer's instructions with appropriate water flushes. The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water.					
If a dose is missed it should be taken as soon as the patient remembers. If it is <12hrs to the next dose the patient should not take the missed dose.					

ELIGIBILITY:

- Indications as above
- Adequate organ function
- **Second line Non-Small Cell Lung Cancer**
  - EGFR T790M mutation positive tumour as demonstrated by a validated test method
  - ECOG status 0-1

EXCLUSIONS:

- Hypersensitivity to osimertinib or any of the excipients
- Pregnancy or breast feeding
- Patients with a past medical history of Interstitial Lung Disease (ILD), drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD
- QT interval (QTc) >470 msec

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- **Second line Non-Small Cell Lung Cancer**
  - Assessment of EGFR T790M mutation status
- FBC, liver renal and bone profile
- ECG to ensure QTc interval less than 470 msec
- Cardiac function (LVEF using ECHO or MUGA scan) if clinically indicated

Regular tests:

- FBC, liver, renal and bone profile.
- ECG at cycle 2 to ensure QTc < 481 msec
- ECG at subsequent cycles (cyle 3+) if clinically indicated
- Cardiac function (LVEF using ECHO or MUGA scan) if clinically indicated

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.
- Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.
- If dose reduction is necessary, then the dose should be reduced to 40 mg taken once daily

Renal and Hepatic Impairment:

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

Renal Impairment		Hepatic Impairment			
CrCl (ml/min)	**Dose**	**AST**		**Bilirubin**	**Dose**
>15	100% dose	>ULN	and/or	≤ULN	100% dose
<15 or dialysis	The safety and efficacy has not been established. Caution should be exercised.	Any	and	<1.5 ULN	100% dose
		Any		1.5-3 ULN	100% dose
		Severe impairment			Not recommended

Management of adverse events:

Table 2: Dose modification of osimertinib for adverse events

Adverse reactions	Recommended dose modification
ILD/Pneumonitis	Permanently discontinue osimertinib
QTc interval > 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is <481 msec or recovery to baseline if baseline QTc is ≥481 msec. Resume dose at 40mg
QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Grade 3* or higher adverse reaction If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Withhold osimertinib for up to 3 weeks Osimertinib may be restarted at the same dose 80mg or a lower dose 40mg Permanently discontinue osimertinib

***National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.**

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low **(Refer to local policy)**

PREMEDICATIONS: Not usually required.

OTHER SUPPORTIVE CARE:

See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse reactions.

Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving osimertinib. Patients should be advised to use effective contraception for the following periods after completion of treatment with this medicinal product: at least 2 months for females and 4 months for males. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details. **Osimertinib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

- **Interstitial Lung Disease (ILD):** Severe, life-threatening or fatal Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g.pneumonitis) have been observed in patients treated with osimertinib in clinical studies. Most cases improved or resolved with interruption of treatment**.** Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD is diagnosed, osimertinib should be permanently discontinued and appropriate treatment initiated as necessary.
- **QTc interval prolongation:** QTc interval prolongation occurs in patients treated with osimertinib. QTc interval prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death.

When possible, the use of osimertinib in patients with congenital long QT syndrome should be avoided. Periodic monitoring with electrocardiograms (ECGs) and electrolytes should be conducted in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Osimertinib should be permanently discontinued in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

- **Left ventricular dysfunction:** Cases of reduction in LVEF were observed during clinical trials. 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.
- **Keratitis:** Patients presenting with signs and symptoms suggestive of keratitis 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.

DRUG INTERACTIONS:

- Strong CYP3A4 inducers can decrease the exposure of osimertinib.
  It is recommended that concomitant use of strong CYP3A inducers (e.g. Phenytoin, rifampicin and carbamazepine) with osimertinib should be avoided. Moderate CYP3A4 inducers may also decrease osimertinib exposure and should be used with caution, or avoided when possible. There are no clinical data available to recommend a dose adjustment of osimertinib.
- Osimertinib may increase the exposure of breast cancer resistant protein (BCRP) and P-glycoprotein (P-gp) substrates.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Osimertinib L01XE35

REFERENCES:

1. Mok TS et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017;376(7):629-640.
2. Osimertinib (Tagrisso®) Summary of Product Characteristics EMA. Last updated: 25/02/2020. Accessed September 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	15/06/2020		Dr Janice Walshe
2	9/9/2020	Updated baseline/regular cardiac tests	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.