Osimertinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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
First-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.	C34	00353b	CDS 01/10/2020
As monotherapy for adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA Non-Small Cell Lung Cancer (NSCLC) whose tumour has epidermal growth factor receptor (EGFR) exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations.	C34	00353c	CDS 01/03/2024

* This is for post 2012 indications only

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.

For metastatic therapy, osimertinib is administered once daily until disease progression or unacceptable toxicity develops.

For adjuvant therapy, treatment with osimertinib should be continued until disease progression or unacceptable toxicity occurs. Treatment duration for more than 3 years was not studied.

Day	Drug	Dose	Route	Cycle
1	Osimertinib	80mg once daily	PO	Continuous
The tablet should be swallowed whole with water and it should not be crushed, split or chewed. Tablet can be taken with or without food at the same time each day.				
If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50mL of non-carbonated 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
- ECOG status 0-1
- **First line locally advanced or metastatic Non-Small Cell Lung Cancer**
  - EGFR mutation status positive tumour as demonstrated by a validated test method
- **Second line locally advanced or metastatic Non-Small Cell Lung Cancer**
  - EGFR T790M mutation positive tumour as demonstrated by a validated test method
- **Adjuvant treatment**
  - EGFR Ex19del or L858R mutation positive tumour as demonstrated by a validated test method
  - Adjuvant therapy with osimertinib to commence within 10 weeks of complete surgical resection if adjuvant chemotherapy not prescribed
  - For patients who are prescribed adjuvant chemotherapy, osimertinib should not be started until after the completion of adjuvant chemotherapy. A minimum of two weeks must have elapsed, and not more than 10 weeks from when the last dose of chemotherapy (comprising platinum-based doublet treatment for a maximum of 4 cycles) is administered

USE WITH CAUTION:

- 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 were excluded from clinical studies. See ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS below
- Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 ms) were excluded from clinical trials. See ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS below
- 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
- Elderly patients (>65 years) or patients with low body weight (<50kg) may be at increased risk of developing grade 3 adverse events and should be monitored closely

EXCLUSIONS:

- Hypersensitivity to osimertinib or any of the excipients
- Patients with congenital long QT syndrome
- Pregnancy or breast feeding
- **Adjuvant treatment**
  - Treatment with any of the following:
    - Neo–adjuvant or adjuvant radiation therapy
    - Neo-adjuvant platinum based or other chemotherapy
    - Prior treatment with EGFR inhibitors

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- Assessment of EGFR mutation status using a validated test method
  - For adjuvant treatment testing should be carried out on tumour resected tissue
- FBC, liver, renal and bone profile
- ECG
- Cardiac function (LVEF using ECHO or MUGA scan) if clinically indicated

Regular tests:

- FBC, liver, renal and bone profile
- ECG at baseline and cycle 2 to ensure QTc not greater than 500 msec
- ECG at subsequent cycles (cycle 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**	
For any grade of renal impairment	No dose adjustment is needed	Mild and moderate or Child-Pugh A/B	No dose adjustment
Haemodialysis	No need for dose adjustment is expected	Severe or Child-Pugh C	50% of the original dose may be considered

Management of adverse events:

Table 2: Dose modification of osimertinib for adverse events

Adverse reactions	Recommended dose modification
Pulmonary ILD/Pneumonitis	Permanently discontinue osimertinib
Cardiac QTc interval > 500 msec on at least 2 separate ECGs QTc interval prolongation with signs/symptoms of serious arrhythmia	Withhold osimertinib until QTc interval is <481 msec or recovery to baseline if baseline QTc is ≥481 msec. Resume dose at 40mg. Permanently discontinue osimertinib
Cutaneous Stevens-Johnson Syndrome and Toxic epidermal necrolysis	Permanently discontinue osimertinib
Blood and lymphatic system Aplastic anaemia	Permanently discontinue osimertinib
Other 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.

- **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.

- **Severe Cutaneous Adverse Reactions (SCARs):** Case reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with frequency categories of rare and not known, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of SJS and TEN. If signs and symptoms suggestive of SJS or TEN appear, osimertinib should be interrupted. Osimertinib should be discontinued immediately if SJS or TEN are diagnosed.
- **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.
- **Aplastic anaemia:** Rare cases of aplastic anaemia, including fatal events, have been reported in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, pallor, infection and fatigue. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anaemia.

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. Concomitant use of St. John's Wort is contraindicated.
- 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.

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. Soria JC et al. Osimertinib in Untreated EGFR-mutated Advanced Non-Small Cell Lung Cancer. N Eng J Med 2018: 378:113-125.
3. Wu YL et al; ADAURA Investigators. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Oct 29; 383(18):1711-1723. doi: 10.1056/NEJMoa2027071. Epub 2020 Sep 19. PMID: 32955177.
4. Tsuboi M et al., ADAURA Investigators. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. N Engl J Med. 2023 Jul 13; 389(2):137-147. doi: 10.1056/NEJMoa2304594. Epub 2023 Jun 4. PMID: 37272535.
5. Roy S et al., Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non–Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. Journal of Clinical Oncology 2023 41:10, 1830-1840. Available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10082285/
6. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
8. Osimertinib (Tagrisso®) Summary of Product Characteristics EMA. Last updated: 20/11/2023. Accessed December 2023. 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	09/09/2020	Updated baseline/regular cardiac tests	Prof Maccon Keane
3	29/09/2020	Regimen review. Addition of 1L indication. Updated Use with Caution.	Dr Emer Hanrahan, Dr Janice Walshe
4	05/10/2021	Regimen review. Updated treatment table.	Prof Maccon Keane
5	01/03/2024	Reviewed regimen. Addition of adjuvant indication. Updated treatment section, eligibility, cautions and exclusions. Updated Baseline tests. Updated Table 1 (renal and hepatic dose modifications). Updated Table 2 and adverse effects in line with SPC updates. Updated drug interactions.	Dr Sinead Noonan

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.