Tepotinib

Indication
Tepotinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations

Regimen details
The recommended dose is 450 mg tepotinib (2 tablets) taken once daily

Cycle frequency
Continuous treatment, supply every 28 days

Number of cycles
Until disease progression or unacceptable toxicity

Administration
The tablet(s) should be taken with food and should be swallowed whole (patients should not crush or chew the tablet before swallowing)

Pre-medication
None

Emetogenicity
Mildly emetogenic, prescribe oral metoclopramide

Additional supportive medication
Loperamide

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days

Liver enzymes (ALT and AST) and bilirubin should be monitored prior to the start of tepotinib, every 2 weeks during the first 3 months of treatment, then once a month

Investigations –pre subsequent cycles
FBC, U+E (including creatinine), LFT (including AST)

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 30 mL/min

Bilirubin	≤ 2 x ULN
AST	< 3 x ULN

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like adverse reactions (for example, pneumonitis) have been reported, including a fatal case.

Patients should be monitored for new or worsening pulmonary symptoms indicative for ILD-like reactions (for example, dyspnoea, cough, fever). Tepotinib should be withheld immediately; and patients should be promptly investigated for alternative diagnosis or specific aetiology of interstitial lung disease. Tepotinib must be permanently discontinued if interstitial lung disease is confirmed and the patient be treated according to local clinical practice

Interpretation of laboratory tests

Nonclinical studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporters (MATE) 1 and 2. Creatinine is a substrate of these transporters, and the observed increases in creatinine may be the result of inhibition of active tubular secretion rather than renal injury. Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution considering this effect

Dose modifications

Renal impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance 30 to 89 mL/min). The pharmacokinetics and safety of tepotinib in patients with severe renal impairment (creatinine clearance below 30 mL/min) have not been studied.

Hepatic impairment

No dose adjustment is recommended in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment. The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child Pugh Class C) have not been studied.

Adverse reaction	**Severity**	**Dose modification**
Interstitial Lung Disease (ILD)	Any grade	Withhold tepotinib if ILD is suspected. Permanently discontinue tepotinib if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin	Grade 3	Withhold tepotinib until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume tepotinib at the same dose; otherwise resume tepotinib at a reduced dose.
	Grade 4	Permanently discontinue tepotinib.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or haemolysis	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue tepotinib.
Increased total bilirubin without concurrent increased ALT and/or AST	Grade 3	Withhold tepotinib until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume tepotinib at a reduced dose; otherwise permanently discontinue.
	Grade 4	Permanently discontinue tepotinib.
Other adverse reactions	Grade 2	Maintain dose level. If intolerable, consider withholding tepotinib until resolved, then resume tepotinib at a reduced dose.

Adverse reaction	Severity	Dose modification
	Grade 3	Withhold tepotinib until resolved, then resume tepotinib at a reduced dose.
	Grade 4	Permanently discontinue tepotinib.

Adverse effects –

for full details consult product literature/ reference texts

Hypoalbuminaemia
Interstitial lung disease
Nausea
Diarrhoea
Abdominal pain
Constipation
Vomiting
Increased liver enzymes
Oedema
Fatigue
Raised creatinine
Raised amylase
Raised lipase

Significant drug interactions

– for full details consult product literature/ reference texts

CYP inducers and P-gp inducers
Tepotinib is a substrate for P-glycoprotein (P-gp). Strong P-gp inducers may have the potential to decrease tepotinib exposure. Strong CYP inducers may also decrease tepotinib exposure. Concomitant use of strong CYP inducers and P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided.

Dual strong CYP3A inhibitors and P-gp inhibitors
The effect of strong CYP3A inhibitors or P-gp inhibitors on tepotinib has not been studied clinically. However, metabolism and in vitro data suggest concomitant use of medicinal products that are strong CYP3A inhibitors and P gp inhibitors may increase tepotinib exposure, which may increase the incidence and severity of adverse reactions of tepotinib. Concomitant use of tepotinib with dual strong CYP3A and P-gp inhibitors (e.g. itraconazole) should be avoided.

P-gp substrates
Tepotinib can inhibit the transport of sensitive substrates of P gp. Monitoring of the clinical effects of P gp-dependent substances with a narrow therapeutic index (e.g. digoxin) is recommended during co-administration with tepotinib.

BCRP substrates
Tepotinib can inhibit the transport of sensitive substrates of the Breast Cancer Resistance Protein (BCRP). Monitoring of the clinical effects of sensitive BCRP substrates is recommended during co-administration with tepotinib.

Metformin
Based on in vitro data, tepotinib or its metabolite may have the potential to alter the exposure to co-administered metformin in humans through inhibition of metformin's renal excretion or hepatic uptake mediated via OCT1 and 2 and MATE1 and 2. Monitoring of the clinical effects of metformin is recommended during co-administration with tepotinib

Additional comments

Embryo-foetal toxicity

Tepotinib can cause foetal harm when administered to pregnant women.

Women of childbearing potential or male patients with female partners of childbearing potential should be advised of the potential risk to a foetus.

Women of childbearing potential should use effective contraception during tepotinib treatment and for at least 1 week after the last dose.

Male patients with female partners of childbearing potential should use barrier contraception during Tepotinib treatment and for at least 1 week after the last dose

References

Tepotinib EAMS protocol - https://www.gov.uk/government/publications/tepotinib-in-the-treatment-of-advanced-non-small-cell-lung-cancer-nsclc/tepotinib-treatment-protocol-information-for-healthcare-professionals

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THIS PROTOCOL HAS BEEN DIRECTED BY DR LAU, DESIGNATED LEAD CLINICIAN FOR LUNG CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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