Sotorasib (Lung)

Indication

Advanced non-small cell lung cancer (NSCLC) exhibiting a KRAS G12C mutation, previously treated with at least one prior systemic therapy in the advanced setting:

- Platinum doublet chemotherapy **and/or** PD-1/PD-L1 targeted immunotherapy
  and
- All appropriate and commissioned targeted treatment for any other actionable mutations (including EGFR, ALK, ROS1, BRAF V600E, MET exon 14 skipping alteration, RET)

KRAS G12C mutations are identified in 13.1% of non-squamous NSCLC and 1.9% of squamous NSCLC. KRAS is reflex tested for all non-squamous NSCLC in the South West as part of the NGS panel, and can be requested for squamous NSCLC if high clinical suspicion.

(NICE TA781)

ICD-10 codes

C34

Regimen details

Drug	Dose	Route
Sotorasib	960mg OD	Oral

Cycle frequency

Continuous

Number of cycles

Until disease progression or unacceptable toxicity

Administration

Sotorasib is available as 120mg tablets. Tablets should normally be swallowed whole with water, with or without food.

Tablets may be dispersed in 120mL of non-carbonated, room-temperature water, without crushing. The mixture should be stirred until the tablets are dispersed into small pieces (the tablet will not completely dissolve) and drunk immediately. The appearance of the mixture may range from pale to bright yellow. The container must be rinsed with an additional 120mL of water, which should be drunk immediately. If not drunk immediately, the mixture must be stirred again to ensure that the tablets are dispersed. The dispersion must be discarded if it is not drunk within 2 hours.

Sotorasib should be taken at approximately the same time each day. If a dose is missed and less than 6 hours have passed since the scheduled time of dosing, then the dose can be taken as normal. If more than 6 hours have passed since the scheduled time of dosing, the dose should not be taken. Treatment should continue as prescribed the next day. Additional doses should not be taken in place of a missed dose. If vomiting occurs after taking a dose, an additional dose must not be taken on the same day and treatment can continue as prescribed the following day.

If a patient is also taking a PPI or H2 receptor antagonist, sotorasib should be taken 4 hours before or 10 hours after administration of the antacid.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential – refer to local policy

Additional supportive medication
Loperamide as required

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Blood pressure	Baseline

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U&E (including creatinine)	Monthly
LFTs	3 weekly during first 3 months then monthly
Calcium	Monthly
Blood pressure	Monthly or as clinically indicated

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

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	≥ 60ml/min
AST/ALT	< 2.5 x ULN
Bilirubin	< 1.5 x ULN

Dose modifications

Dose level	Sotorasib Dose
Full dose	960mg OD
First dose reduction	480mg OD
Second dose reduction	240mg OD

Sotorasib should be discontinued if patients are unable to tolerate the minimum dose of 240mg OD

- **Haematological toxicity**

Sotorasib is not myelosuppressive and may be continued during periods of mild myelosuppression.

- **Renal impairment**

No dose adjustment is required in mild renal impairment (>60ml/min). Sotorasib has not been studied in moderate or severe renal impairment, but is minimally renally excreted.

- **Hepatic impairment**

No dose adjustment is required for mild hepatic impairment (AST/ALT < 2.5 x ULN and bilirubin <1.5 x ULN). Sotorasib has not been studied in moderate or severe hepatic impairment.

- **Other toxicities**

Toxicity	Definition	Action/Dose adjustment
Hepatotoxicity	Grade 2 rise in AST/ALT with symptoms *Or* Grade ≥ 3 rise in AST/ALT	Stop treatment until recovered to ≤ grade 1 or baseline grade After recovery, resume treatment at next dose reduction level.
	AST/ALT > 3 x ULN and bilirubin > 2 x ULN, in the absence of alternative causes	Permanently discontinue treatment
Interstitial lung disease (ILD)/ Pneumonitis	Any grade	Stop treatment if ILD/pneumonitis is suspected. Permanently discontinue if ILD/pneumonitis is confirmed
Nausea or vomiting despite appropriate supportive care	Grade 3 to 4	Stop treatment until recovered to ≤ grade 1 or baseline grade After recovery, resume treatment at next dose reduction level.
Diarrhoea despite appropriate supportive care	Grade 3 to 4	Stop treatment until recovered to ≤ grade 1 or baseline grade After recovery, resume treatment at next dose reduction level.
Hypertension	Grade 2 • Systolic blood pressure (SBP) 140 - 159 mm Hg or diastolic blood pressure (DBP) 90 - 99 mm Hg if previously within normal limits. • Change in baseline medical intervention indicated. • Recurrent or persistent (≥ 24 hrs). • Symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg. • Monotherapy indicated initiated	Proceed with treatment and inform clinical team. Consider referral to GP for monitoring and management of hypertension. Perform urinalysis to check for proteinuria

Hypertension (cont'd)	Grade 3 • SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg. • Medical intervention indicated. • More than one drug or more intensive therapy than previously used indicated	Stop treatment until recovered to ≤ grade 1 (SBP120-139mmHg or DBP to 80-89mmHg) or baseline grade Perform urinalysis to check for proteinuria After recovery, resume treatment at next dose reduction level. If grade 4 hypertension recurs, treatment should be permanently discontinued.
	Grade 4 (e.g. hypertensive crisis)	
Proteinuria	Grade 3 to 4 4+ proteinuria or urinary protein ≥2.5g/24 hrs	Stop treatment until recovered to ≤ grade 1 (1+ proteinuria; urinary protein ≥ULN to < 1g/24 hrs) After recovery, resume treatment at next dose reduction level.
Other adverse reactions	Grade 3 to 4	Stop treatment until recovered to ≤ grade 1 or baseline grade After recovery, resume treatment at next dose reduction level.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Interstitial lung disease/pneumonitis - more frequent in patients previously exposed to radiotherapy or immunotherapy
Hepatitis

- **Frequently occurring side effects**

Anaemia
Headache
Dyspnoea
Cough
Diarrhoea
Nausea, vomiting
Abdominal pain
Constipation
Deranged LFTs
Fatigue
Pyrexia
Arthralgia, myalgia
Proteinuria
Peripheral oedema

- **Other side effects**

Hypocalcaemia, hypokalaemia, hyponatraemia
Hypertension

Significant drug interactions – for full details consult product literature/ reference texts

Acid reducing agents - co-administration of sotorasib with a PPI or H2 receptor antagonist lead to a decrease in sotorasib concentrations therefore co-administration is not recommended as impact on the efficacy of sotorasib is unknown. If treatment with an acid-reducing agent is required, Sotorasib should be taken 4 hours before or 10 hours after administration of a local antacid.
Strong CYP3A4 inducers e.g. rifampicin – reduces sotorasib levels
CYP3A4 substrates e.g. midazolam, simvastatin, felodipine – reduced plasma concentrations of substrate, avoid co-administration if substrate has narrow therapeutic index or adjust substrate dosage
P-glycoprotein (P-gp) substrates e.g. digoxin, dabigatran, colchicine, fexofenadine – increased concentrations of substrate, avoid co-administration if possible or consider decreasing P-gp substrate dose

Additional comments

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

There is no data on the use of Sotorasib in pregnant women, animal studies report reproductive toxicity. It is unknown if Sotorasib is excreted in breast milk, and breast feeding should be avoided. No data on effects on fertility.

References

- National Institute for Health and Care Excellence (NICE TA781) accessed 7th April 2022 via www.nice.org.uk
- Summary of Product Characteristics – Sotorasib (Amgen) accessed 7th April 2022 via www.medicines.org.uk
- Skoulidis, F. *et al.* Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med 2021;384:2371-2381

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