Sotorasib

Indication
Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy

Regimen details
Sotorasib 960 mg (eight 120 mg tablets) orally once daily, at the same time each day, with or without food

Cycle frequency
Continuous treatment (supply monthly)

Number of cycles
Continue until disease progression or unacceptable toxicity

Administration
If less than 6 hours have passed since the scheduled time of dosing, the patient should take the dose as normal. If more than 6 hours have passed since the scheduled time of dosing, the patient must not take the dose. Treatment should be continued as prescribed the next day. Additional doses should not be taken in place of a missed dose.

If vomiting occurs after taking sotorasib, the patient must not take an additional dose on the same day, and treatment must be continued as prescribed the next day

Administration to patients who have difficulty swallowing solids
Patients should disperse tablets in 120 mL of non-carbonated, room-temperature water without crushing. Other liquids must not be used. Patients should stir until tablets are dispersed into small pieces (the tablet will not completely dissolve) and drink immediately. The appearance of the mixture may range from pale to bright yellow. The container must be rinsed with an additional 120 mL of water, which should be drunk immediately. If it is not drunk immediately, patients must stir again to ensure that the tablets are dispersed. The dispersion must be discarded if it is not drunk within 2 hours.

Pre-medication
N/A

Emetogenicity – consult anti-emetic policy for full details
Minimum Risk (Category D)

Additional supportive medication
Supply metoclopramide and loperamide with cycle 1

Extravasation
N/A

Investigations – pre first cycle

Table 1 - Standard Investigations prior to first cycle

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

Investigations –pre subsequent cycles

LFT (ALT, AST & Bilirubin) every 2 weeks for the first 3 months followed by each cycle (or as clinically indicated)

FBC each cycle

U+E (including creatinine) each cycle

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Table 2 – Standard test result limits for each administration to go ahead

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST/ALT	< 3 x ULN

Dose modifications

Table 3 – Recommended dose reduction levels

Dose reduction level	Dose
First dose reduction	480 mg (four 120 mg tablets) once daily
Second dose reduction	240 mg (two 120 mg tablets) once daily

Table 4 – Recommended dose modifications

Adverse reaction	Severity	Dose modification
Hepatotoxicity	Grade 2 AST or ALT with symptoms or Grade ≥ 3 AST or ALT	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
	AST or ALT > 3 × ULN with total bilirubin > 2 × 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 (including anti-emetic therapy)	Grade 3 to 4	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
Diarrhoea despite appropriate supportive care (including anti-diarrhoeal therapy)	Grade 3 to 4	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
Other adverse reactions	Grade 3 to 4	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level

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

- **Serious side effects**

Hepatotoxicity
Interstitial lung disease

- **Frequently occurring side effects**

Nausea
Diarrhoea
Fatigue
Vomiting
Anaemia
Hypokalaemia
Rash

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

Acid-reducing agents

Co-administration of sotorasib with a PPI (omeprazole) or an H2 receptor antagonist (famotidine) led to a decrease in sotorasib concentrations.

Under fed conditions (standard-calorie moderate-fat meals), co-administration of multiple doses of omeprazole with a single dose of 960 mg sotorasib decreased sotorasib Cmax by 65% and AUC by 57%. Co-administration of a single dose of famotidine given 10 hours prior and 2 hours after a single dose of 960 mg sotorasib decreased sotorasib Cmax by 35% and AUC by 38%.

Under fasted conditions, co-administration of multiple doses of omeprazole with a single dose of 960 mg sotorasib decreased sotorasib Cmax by 57% and AUC by 42%.

Co-administration of PPIs and H2 receptor antagonists with LUMYKRAS is not recommended because the impact on sotorasib efficacy is unknown. If treatment with an acid-reducing agent is required, LUMYKRAS should be taken 4 hours before or 10 hours after administration of a local antacid (see section 4.2).

Strong CYP3A4 inducers

Co-administration of sotorasib with multiple doses of a strong CYP3A4 inducer (rifampicin) decreased sotorasib Cmax by 35% and AUC by 51%. Co-administration of strong CYP3A4 inducers with LUMYKRAS is not recommended because the impact on sotorasib efficacy is unknown.

Effect of sotorasib on other medicinal products

CYP3A4 substrates

Sotorasib is a moderate CYP3A4 inducer. Co-administration of sotorasib with CYP3A4 substrates led to a decrease in their plasma concentrations, which may reduce the efficacy of these substrates.

Co-administration of sotorasib with midazolam (a sensitive CYP3A4 substrate) decreased midazolam Cmax by 48% and AUC by 53%.

Avoid co-administration of sotorasib with CYP3A4 substrates with narrow therapeutic indices. If co-administration cannot be avoided, adjust the CYP3A4 substrate dosage in accordance with the current summary of product characteristics.

Transporter systems

P-glycoprotein (P-gp) Substrates

Coadministration of sotorasib with digoxin (a P-gp substrate) increased digoxin Cmax by 91% and AUC by 21%.

Avoid coadministration of sotorasib with P-gp substrates, for which minimal concentration changes may lead to serious

toxicities. If coadministration cannot be avoided, decrease the P-gp substrate dosage in accordance with its Prescribing Information.

In vitro data indicated that sotorasib may have the potential to inhibit Breast Cancer Resistance Protein (BCRP); the clinical relevance of these findings is unknown.

Additional comments

References

1. LUMYKRAS SPC https://www.medicines.org.uk/emc/product/12871 updated 08/09/2021, Accessed 31/12/2021

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

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE