# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1 NAME OF THE MEDICINAL PRODUCT

Hyrnuo 10 mg film-coated tablets.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of sevabertinib.

Excipient(s) with known effect

Each film-coated tablets contains 34.79 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

Red brown film-coated, round, biconvex tablets with a diameter of 6 mm, debossed with “SE” on one side and “10” on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hyrnuo as monotherapy is indicated for the treatment of adult patients with advanced non-squamous non-small cell lung cancer (NSCLC) whose tumours have *HER2* (*ERBB2*) tyrosine kinase domain activating mutations and who have received a prior systemic therapy.

## 4.2 Posology and method of administration

Hyrnuo therapy should be initiated and supervised by physicians experienced in the
use of anti-cancer therapies.

Patient selection
The presence of *HER2 (ERBB2)* tyrosine kinase domain (TKD) activating mutations in tumour specimens must be confirmed using a validated test prior to initiation of therapy with Hyrnuo.

Posology
*Adults*
The recommended dose of Hyrnuo is 20 mg (two 10 mg tablets) taken twice a day until disease progression or unacceptable toxicity.

If vomiting occurs after taking Hyrnuo, the patient must not take an additional dose.
The next dose should be taken at its scheduled time.

*Missed Dose*
If a dose of Hyrnuo is missed, the dose should be taken as soon as the patient remembers prior to the next scheduled dose, but not within 30 minutes of the next scheduled dose. The patient should not take two doses together to make up for a missed dose.

*Dose Modifications due to Adverse Reactions*
Management of adverse reactions may require dose interruption, dose reduction and / or discontinuation of Hyrnuo. The recommended dose reduction levels are outlined in Table 1. Patients who are unable to tolerate 10 mg once daily should discontinue Hyrnuo treatment permanently.

**Table 1: Recommended Dose Reductions for Hyrnuo for Adverse Reactions**

| **Dose Reduction** | **Number of Tablets and Frequency** | **Total Daily Dose** |
|---|---|---|
| First dose reduction | One 10 mg tablet twice daily | 20 mg |
| Second dose reduction | One 10 mg tablet once daily | 10 mg |

The recommended dose modifications and measures for adverse reactions are provided in Table 2 (see also sections 4.4 and 4.8).

**Table 2: Recommended Dose Modifications for Hyrnuo for Adverse Reactions**

| **Adverse Reaction** | **Severity[a]** | **Recommended Hyrnuo dose modification and measures** |
|---|---|---|
| Diarrhoea | Intolerable or | - Withhold Hyrnuo until recovery to Grade ≤1. |

| **Adverse Reaction** | **Severity[a]** | **Recommended Hyrnuo dose modification and measures** |
|---|---|---|
| (see section 4.4) | recurrent Grade 2 | - Resume Hyrnuo at the same dose or the next lower dose as clinically appropriate. |
| | Grade 3 | - Withhold Hyrnuo until recovery to Grade ≤1.<br>- For first occurrence, resume Hyrnuo at the same dose or the next lower dose.<br>- For re-occurrence, resume Hyrnuo at the next lower dose. |
| | Grade 4 | - Permanently discontinue Hyrnuo. |
| Liver enzyme elevation (see section 4.4) | Grade 2, 3 or 4 ALT and/or AST *without* increased total bilirubin or Grade 3 total bilirubin | - Interrupt Hyrnuo until recovery to ≤ Grade 1 or baseline.<br>- Resume Hyrnuo at the next lower dose. |
| | ALT or AST ≥ 3× ULN *with* total bilirubin ≥ 2× ULN or Grade 4 total bilirubin | - Permanently discontinue Hyrnuo. |
| Interstitial lung disease (ILD)/ pneumonitis (see section 4.4) | Any Grade | - Permanently discontinue Hyrnuo. |
| Ocular toxicity (see section 4.4) | Intolerable or recurrent Grade 2 | - Withhold Hyrnuo until recovery to Grade ≤1.<br>- Resume Hyrnuo at the same dose or the next lower dose as clinically appropriate. |
| | Grade 3 | - Withhold Hyrnuo until recovery to Grade ≤1.<br>- For first occurrence, resume Hyrnuo at the same dose or the next lower dose.<br>- For re-occurrence, resume Hyrnuo at the next lower dose. |
| | Grade 4 | - Permanently discontinue Hyrnuo. |
| Pancreatic enzyme elevations (see section 4.4) | Intolerable or recurrent Grade 2 | - Withhold Hyrnuo until recovery to Grade ≤1.<br>- Resume Hyrnuo at the same dose or the next lower dose as clinically appropriate. |
| | Grade 3 | - Withhold Hyrnuo until recovery to Grade ≤1.<br>- For first occurrence, resume Hyrnuo at the same dose or the next lower dose. |

| Adverse Reaction | Severity[a] | Recommended Hyrnuo dose modification and measures |
|---|---|---|
| | | - For re-occurrence, resume Hyrnuo at the next lower dose. |
| | Grade 4 | - Permanently discontinue Hyrnuo. |
| Other adverse reactions | Intolerable or recurrent Grade 2 | - Withhold Hyrnuo until recovery to Grade ≤1.<br>- Resume Hyrnuo at the same dose or the next lower dose as clinically appropriate. |
| | Grade 3 | - Withhold Hyrnuo until recovery to Grade ≤1.<br>- For first occurrence, resume Hyrnuo at the same dose or the next lower dose.<br>- For re-occurrence, resume Hyrnuo at the next lower dose. |
| | Grade 4 | - Permanently discontinue Hyrnuo. |

[a] Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0

*Dose Modifications due to concomitant use with strong CYP3A4 inhibitors*
Concomitant use of strong CYP3A4 inhibitors with Hyrnuo is not recommended. If concomitant use cannot be avoided, the current Hyrnuo total daily dose should be reduced by 50% as shown in Table 3 below (see also section 4.5). For patients taking a current total daily dose of 10 mg (one 10 mg tablet once daily) (refer to 'Dose Modifications due to Adverse Reactions' information under current section 4.2), Hyrnuo should be temporarily withheld until treatment with the strong CYP3A4 inhibitor is completed.
After the CYP3A4 inhibitor has been discontinued for 3 to 5 elimination half-lives, Hyrnuo should be resumed at the dose taken prior to initiating the inhibitor.

**Table 3: Recommended Dose Reductions of Hyrnuo for Concomitant Use of Strong CYP3A4 Inhibitors**

| Current Hyrnuo Dosage | Adjusted Hyrnuo Dosage |
|---|---|
| Two 10 mg tablets twice daily<br>(total daily dose of 40 mg) | One 10 mg tablet twice daily<br>(total daily dose of 20 mg) |
| One 10 mg tablet twice daily<br>(total daily dose of 20 mg) | One 10 mg tablet once daily<br>(total daily dose of 10 mg) |
| One 10 mg tablet once daily<br>(total daily dose of 10 mg) | Withhold Hyrnuo |

Special populations
*Paediatric population*
Safety and efficacy of Hyrnuo in children and adolescents below 18 years of age have not been established.

*Elderly*
No dose adjustment is necessary in patients 65 years of age or older (see also section 5.2).

*Hepatic Impairment*
Use in patients with moderate and severe hepatic impairment is not recommended.

No dose adjustment is necessary for patients with mild hepatic impairment (total bilirubin ≤ 1.5 x ULN and any AST) (see section 5.2).

The pharmacokinetics of sevabertinib have not been studied in patients with moderate (total bilirubin >1.5 to ≤3 x ULN and any AST) or severe (total bilirubin >3 x ULN and any AST) hepatic impairment.

*Renal Impairment*
No dose adjustment is considered necessary in patients with renal impairment (see section 5.2).

The pharmacokinetics of sevabertinib have not been studied in patients with severe renal impairment (eGFR less than 30 mL/min).

Method of administration
For oral use.

The tablets should be taken with food.

The tablets should be swallowed whole and should not be chewed, crushed, or split prior to swallowing.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.

## 4.4 Special warnings and precautions for use

Diarrhoea

Diarrhoea has been reported during treatment with Hyrnuo and can be severe, leading to dehydration and electrolyte imbalance, including hypokalaemia which may lead to cardiac arrhythmias, if untreated. Diarrhoea usually occurred within the first week of treatment (see section 4.8).

Patients should be advised to start an antidiarrhoeal agent (e.g. loperamide), and to increase fluid and electrolyte intake at first sign of diarrhoea or increased bowel movement frequency. Based on the severity of the diarrhoea, patients may require temporary interruption, dose reduction or permanent discontinuation of therapy with Hyrnuo (refer to 'Dose Modifications due to Adverse Reactions' information under section 4.2).

Liver enzyme elevation

Increase in ALT and/or AST have been reported during treatment with Hyrnuo (see section 4.8).

Monitor liver function tests including ALT, AST, and total bilirubin at baseline prior to initiation of Hyrnuo, and monthly thereafter as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Based on the severity of the adverse reaction, treatment with Hyrnuo should be interrupted, then dose reduced or permanently discontinued (see section 4.2).

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis has been reported in patients treated with Hyrnuo (see section 4.8). Patients with a history of steroid-dependent ILD/pneumonitis have not been studied.

Patients should be monitored for symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever). Hyrnuo should be permanently discontinued in patients with confirmed ILD/pneumonitis (see section 4.2).

Ocular toxicity

Ocular toxicity has been reported in patients treated with Hyrnuo (see section 4.8).

Patients presenting with new or worsening eye symptoms should promptly be referred to an ophthalmologist. Based on the severity of the adverse reaction, treatment with Hyrnuo should be interrupted, then dose reduced or permanently discontinued (see section 4.2).

Pancreatic enzyme elevations

Elevations in amylase and lipase levels have been reported during treatment with Hyrnuo (see section 4.8).

Amylase and lipase should be monitored regularly during treatment with Hyrnuo. Based on the severity of the adverse reaction, treatment with Hyrnuo should be interrupted, then dose reduced or permanently discontinued (see section 4.2).

Embryo-foetal toxicity

Based on findings from animal studies and its mechanisms of action, Hyrnuo may cause foetal harm when administered to pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant and to use highly effective contraception during treatment and for 1 week after the last dose of Hyrnuo (see section 4.6).

Male patients with female partners of childbearing potential should also be advised to use highly effective contraception during treatment with Hyrnuo and for 1 week after the last dose to prevent pregnancy. If a male patient is engaged in sexual activity with

a pregnant woman, a condom is required during treatment and for 1 week after the last dose of Hyrnuo (see section 4.6).

Information about excipients

Hyrnuo contains lactose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of CYP3A4 inhibitors on sevabertinib

*Strong CYP3A4 inhibitors*

Co-administration of multiple daily doses of itraconazole (200 mg), a strong CYP3A4 inhibitor, and sevabertinib (10 mg) increased sevabertinib exposure with a mean AUC ratio of 2.3 (reflecting a 130% increase) and a mean $C_{max}$ ratio of 1.6 (reflecting a 60% increase) compared with administration of sevabertinib alone.

Concomitant use of strong CYP3A4 inhibitors (including, but not limited to, clarithromycin, itraconazole, ketoconazole, cobicistat, lopinavir/ritonavir, saquinavir/ritonavir, grapefruit or grapefruit juice) during treatment with Hyrnuo is not recommended.

If concomitant use cannot be avoided, the Hyrnuo dose should be modified as recommended (refer to 'Dose Modifications due to concomitant use with strong CYP3A4 inhibitors' information under section 4.2).

*Moderate CYP3A4 inhibitors*

Limited clinical data are available on the impact of concomitant use of moderate CYP3A4 inhibitors on sevabertinib plasma concentrations. As sevabertinib exposure may be increased when co-administered with moderate CYP3A4 inhibitors, it is recommended to closely monitor patients for adverse reactions (see section 4.8).

*Weak CYP3A4 inhibitors*

Based on a population pharmacokinetic analysis, no impact of concomitant use of weak CYP3A4 (and P-gp) inhibitors was found. This indicates that Hyrnuo may be given concomitantly with weak CYP3A4 inhibitors without a clinically relevant drug-drug interaction.

Effects of CYP3A4 inducers on sevabertinib

Co-administration of multiple doses of carbamazepine (600 mg), a strong CYP3A4 (and P-gp) inducer, and sevabertinib (40 mg), resulted in a decrease of 79% in mean AUC and a decrease of 57% in $C_{max}$ of sevabertinib.

The effect of moderate CYP3A4 inducers on sevabertinib pharmacokinetics is unknown.

Use of strong CYP3A4 inducers (including, but not limited to, carbamazepine, phenytoin, rifabutin, rifampicin, St. John's Wort) during treatment with Hyrnuo is not recommended since decreased sevabertinib plasma concentrations are expected to result in reduced efficacy. Selection of an alternate concomitant medicinal product, with no or less potential to induce CYP3A4 should be considered.

Effects of P-gp and BCRP inhibitors on sevabertinib

Sevabertinib is a substrate of P-glycoprotein (P-gp), and Breast Cancer Resistance Protein (BCRP) *in vitro*.

No clinically relevant interaction with P-gp or BCRP inhibitors is expected due to high permeability and limited unchanged excretion of sevabertinib.

Effects of acid reducing agents on sevabertinib

Co-administration of multiple doses of esomeprazole (40 mg), a proton pump inhibitor (PPI) and sevabertinib (20 mg) demonstrated no clinically relevant effect on the exposure of sevabertinib (decrease of 10% in mean AUC).

This indicates that Hyrnuo may be given concomitantly with acid-reducing agents (e.g. proton pump inhibitors, H2-receptor antagonists, and locally acting antacids).

Effects of sevabertinib on CYP3A4 substrates

Sevabertinib is a weak inhibitor of CYP3A4.

Co-administration of multiple daily doses of sevabertinib (20 mg twice daily) and midazolam, a sensitive CYP3A4 substrate, increased midazolam exposure with a mean AUC ratio of 1.95 (reflecting a 95% increase) and a mean $C_{max}$ ratio of 1.8 (reflecting an 80% increase) compared with administration of midazolam alone.

This indicates that concomitant use of Hyrnuo may increase the plasma concentrations of sensitive CYP3A4 substrates. Therefore, the related recommendation in the product information of sensitive CYP3A4 substrates with a narrow therapeutic window (including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) should be followed when co-administered with Hyrnuo.

Effects of sevabertinib on CYP1A1 substrates

Sevabertinib is a strong inhibitor of CYP1A1 at clinically relevant concentrations *in vitro*.

This indicates that co-administration of Hyrnuo may increase the plasma concentrations of CYP1A1 substrates. Therefore, the related recommendation in the product information of these substrates (e.g. riociguat, granisetron) should be followed when co-administered with Hyrnuo.

Effects of sevabertinib on P-gp substrates
Sevabertinib is an inhibitor of P-gp.

Co-administration of multiple daily doses of sevabertinib (20 mg twice daily) and dabigatran etexilate, a sensitive P-gp substrate, increased dabigatran exposure with a mean AUC ration of 1.4 (reflecting a 40% increase) while $C_{max}$ was unchanged compared with administration of dabigatran etexilate alone.

This indicates that concomitant use of Hyrnuo may increase the plasma concentrations of sensitive P-gp substrates. Therefore, the related recommendation in the product information of sensitive P-gp substrates with a narrow therapeutic window (including but not limited to digoxin) should be followed when co-administered with Hyrnuo.

Effects of sevabertinib on BCRP substrates
Sevabertinib is an inhibitor of Breast Cancer Resistance Protein (BCRP).

Co-administration of multiple daily doses of sevabertinib (20 mg twice daily) and rosuvastatin, a sensitive BCRP substrate, increased rosuvastatin exposure with a mean AUC ratio of 1.3 (reflecting a 30% increase) and a mean $C_{max}$ ratio of 1.4 (reflecting a 40% increase) compared with administration of rosuvastatin alone.

This indicates that concomitant use of Hyrnuo may increase the plasma concentrations of sensitive BCRP substrates. Therefore, the related recommendation in the product information of sensitive BCRP substrates (including but not limited to methotrexate, atorvastatin) should be followed when co-administered with Hyrnuo.

Effects of sevabertinib on Multidrug and Toxin Extrusion (MATE) 1 and 2-K substrates
Sevabertinib is an inhibitor of MATE1 and MATE2-K at clinically relevant concentrations *in vitro*.

This indicates that co-administration of Hyrnuo may affect renal clearance of substrates of these transporters. Therefore, the related recommendation in the product information of these substrates (including but not limited to metformin, cisplatin) should be followed when co-administered with Hyrnuo.

Effects of sevabertinib on other CYP substrates
Sevabertinib is a weak inhibitor of CYP2C8 at clinically relevant concentrations *in vitro*. The clinical relevance of these findings is unknown.

Sevabertinib does not inhibit CYP2A6, CYP2C9, CYP1A2, CYP2B6, CYP2D6, CYP2C19, and CYP2E1 at clinically relevant concentrations *in vitro*.

Sevabertinib does not induce CYP1A2, CYP2B6, and CYP2C19 at clinically relevant concentrations *in vitro.*

Effects of sevabertinib on other transporter substrates
Sevabertinib did not inhibit Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3, Multidrug Resistance-associated Protein (MRP) 2, Organic Anion Transporter (OAT) 1, Organic Cation Transporter (OCT) 1 and 2 at clinically relevant concentrations *in vitro.*

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential or male patients with female partners of childbearing potential must be informed that Hyrnuo may cause foetal harm (see section 5.3).

The pregnancy status of women of childbearing potential should be verified prior to initiation of Hyrnuo.

Women of childbearing potential should be advised to avoid becoming pregnant and to use highly effective contraception during treatment with Hyrnuo and for 1 week after treatment.

Male patients with female partners of childbearing potential should also be advised to use highly effective contraception during treatment with Hyrnuo and for 1 week after treatment to prevent pregnancy.

If a male patient is engaged in sexual activity with a pregnant woman, a condom is required during and for 1 week after completion of treatment with Hyrnuo. Exposure of the foetus to sevabertinib through seminal transfer to the pregnant woman must be avoided, as this could affect development of the foetus.

Pregnancy
There are no data from the use of sevabertinib in pregnant women.

Animal studies do not provide sufficient information with respect to reproductive toxicity (see section 5.3).

The absence of HER2 and/or EGFR signalling has been shown to result in impairment of embryo-foetal development, embryolethality as well as post-natal death in animals.

Based on its mechanism of action and findings in animal models, sevabertinib may cause foetal harm when administered during pregnancy.

Hyrnuo should not be given during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the foetus.

Female patients taking sevabertinib during pregnancy or who become pregnant while taking sevabertinib should be advised of the potential hazard to the foetus.

Breast-feeding
It is unknown whether sevabertinib or its metabolites are excreted in human milk.

In rats, sevabertinib or its metabolites are excreted in milk (see section 5.3).

A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Hyrnuo and for 1 week following the final dose.

Fertility
There are no human data on the effect of sevabertinib on fertility.

Specific studies on fertility have not been performed (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Hyrnuo has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The safety profile of Hyrnuo is based on data from 287 patients with advanced NSCLC harbouring activating *HER2 (ERBB2)* mutations and/or EGFR mutations who had received Hyrnuo at 20 mg twice daily in the single-arm SOHO-01 clinical study (whole study 20 mg BID).

The most common adverse drug reactions (ADRs) observed (≥20%) in patients receiving Hyrnuo at the recommended dose were diarrhoea (86.8%), rash (45.6%), stomatitis (20.2%), paronychia (25.8%).

Grade 3 or 4 ADRs were reported in 32.1% of patients treated with Hyrnuo; Grade 3 ADRs were reported in 30.7%, and Grade 4 ADRs 1.4 % of patients. The most common Grade 3 or 4 ADRs reported with an incidence of ≥2% in patients who received Hyrnuo were diarrhoea (15.3%), hypokalaemia (5.9%), vomiting (3.1%), decreased appetite (2.1%) and nausea (2.1%).

The most common laboratory abnormalities (≥ 2%) worsening from baseline to Grade 3 or 4 were lipase increased (13.4%), potassium decreased (13.3%), sodium decreased (4.6%), lymphocyte count decreased (4.5%), haemoglobin decreased (3.2%), amylase increased (3.2%), alanine aminotransferase (ALT) increased (2.8%), and aspartate aminotransferase (AST) increased (2.5%).

Serious ADRs occurred in 11.1% of patients who received Hyrnuo. The most common serious ADRs reported in ≥2% of patients were diarrhoea (4.2%) and vomiting (2.4%).

Permanent discontinuation due to ADRs occurred in 8 patients (2.8%) who received Hyrnuo. ADRs leading to permanent discontinuations of Hyrnuo were left ventricular dysfunction (0.3%), corneal epithelial microcysts (0.3%), visual acuity reduced (0.3%), hepatic function abnormal (0.3%), electrocardiogram QT prolonged (0.3%), lymphocyte count decreased (0.3%), pain in extremity (0.3%), renal failure (0.3%) and dyspnoea (0.3%).

Dose interruptions due to an ADR occurred in 35.5% of patients who received Hyrnuo. The most frequent (>3%) ADRs leading to dose interruptions were diarrhoea (14.6%), nausea (4.5%), hypokalaemia (4.2%) and vomiting (3.1%).

Dose reductions due to an ADR occurred in 29.6% of patients who received Hyrnuo. The most frequent (>2%) ADRs leading to dose reductions were diarrhoea (13.2%), alanine aminotransferase increased (2.8%), vomiting (2.1%) and stomatitis (2.1%).

Tabulated list of adverse reactions
Adverse reactions reported in the SOHO-01 study (whole study 20 mg BID) are listed in Table 4.
The ADRs are classified according to the MedDRA system organ class and frequency.

Adverse drug reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1 000 to < 1/100; rare: ≥ 1/10 000 to < 1/1 000, very rare (< 1/10 000), and not known (cannot be estimated from available data).

Within each frequency group, adverse drug reactions are presented in order of decreasing seriousness.

**Table 4: Adverse Drug Reactions Reported in SOHO-01 Study (whole study 20 mg BID safety population, N=287)**

| System Organ Class (MedDRA)[a] | Adverse Reaction | Frequency | |
|---|---|---|---|
| | | All Grades | Grades 3 and 4 |
| Gastrointestinal disorders | Diarrhoea | Very common | Very common |
| | Vomiting | Very common | Common |

| System Organ Class (MedDRA)[a] | Adverse Reaction | Frequency | |
|---|---|---|---|
| | | All Grades | Grades 3 and 4 |
| | Nausea | Very common | Common |
| | Stomatitis[b] | Very common | Uncommon |
| | Abdominal pain[c] | Common | |
| Skin and subcutaneous tissue disorders | Rashd | Very common | Common |
| | Paronychia[e] | Very common | Uncommon |
| | Pruritus | Very common | Uncommon |
| | Dry skin[f] | Very common | |
| | Alopecia | Common | |
| | Palmar-plantar erythrodysesthesia syndrome | Common | |
| Metabolism and nutrition disorders | Hypokalaemia | Very common | Common |
| | Decreased appetite | Very common | Common |
| Investigations | Aspartate aminotransferase increased | Very common | Common |
| | Alanine aminotransferase increased | Very common | Common |
| | Weight decreased | Very common | |
| | Lipase increased | Very common | Uncommon |
| | Blood creatine increased | Very common | Uncommon |
| | Amylase increased | Very common | Uncommon |
| | Glucose increased[g,h] | Very common | Uncommon |
| | Magnesium decreased[g] | Very common | Uncommon |
| | Albumin decreased[g] | Very common | Uncommon |
| | Calcium decreased[g] | Very common | Common |
| | Sodium decreased[g] | Very common | Common |
| | Triglycerides increased[g] | Very common | Uncommon |
| | Lymphocyte count decreased[g] | Very common | Common |
| | Alkaline phosphatase increased[g] | Very common | Uncommon |
| | White blood cell decreased[g] | Very common | Common |
| | Bilirubin increased[g] | Very common | Uncommon |
| Blood and lymphatic system disorders | Anaemia | Very common | Common |
| General disorders and | Fatigue[i] | Common | Uncommon |

| System Organ Class (MedDRA)[a] | Adverse Reaction | Frequency | |
|---|---|---|---|
| | | All Grades | Grades 3 and 4 |
| Administration site conditions | | | |
| Cardiac disorders | Cardiac arrhythmia[j] | Common | Common |
| Eye disorders | Ocular toxicity[k] | Common | Uncommon |
| Respiratory, thoracic and mediastinal disorders | ILD/pneumonitis | Uncommon | Uncommon |

[a] Graded per NCI CTCAE version 5
[b] Stomatitis includes cheilitis, mouth ulceration, mucosal inflammation stomatitis
[c] Abdominal pain includes abdominal distention, abdominal pain, abdominal pain upper
[d] Rash includes acne, acne varioliformis, dermatitis acneiform, eczema, erythema, folliculitis, rash, rash erythematous, rash maculopapular, rash pruritic, skin exfoliation
[e] Paronychia includes ingrowing nail, nail disorder, nail infection, onychalgia, onychoclasis onycholysis, onychomadesis, paronychia
[f] Dry skin includes dry skin, xeroderma
[g] The incidence is based on values reported as laboratory abnormalities (worsening from baseline). The denominator used to calculate the rate varied from 223 to 285 based on the number of patients with a baseline value and at least one post-treatment value.
[h] Graded per NCI CTCAE version 4.03 using only numeric values.
[i] Fatigue includes asthenia, fatigue
[j] Cardiac arrhythmia includes arrhythmia, atrioventricular block complete, electrocardiogram QT prolonged, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia
[k] Ocular toxicity includes blindness unilateral, corneal epithelial microcysts, dry eye, ocular toxicity, visual acuity reduced, visual impairment, xerophthalmia

Description of selected adverse reactions

*Diarrhoea*

In SOHO-01 whole study 20 mg BID safety population, diarrhoea was reported in 86.8% of patients treated with Hyrnuo. Grade 3 diarrhoea was reported in 15.3% of patients. No grade 4 diarrhoea was reported.

The median time to first onset of any grade diarrhoea was 4 days. Dose interruptions occurred in 14.6% of patients, and dose reductions occurred in 13.2% of patients. No treatment discontinuations due to diarrhoea were reported. Among patients with treatment-emergent diarrhoea, 74.8% received anti-diarrhoeal medication, predominantly loperamide or loperamide hydrochloride.

*Rash*

In SOHO-01 whole study 20 mg BID safety population, rash was reported in 65.2% of patients. treated with Hyrnuo and was mild to moderate in severity (Grades 1: 48.4%, Grade 2: 15.7% and Grade 3: 1.0%). No grade 4 rash was reported. Dose interruptions occurred in 2.8% of patients and dose reductions occurred in 1.7% of patients. No treatment discontinuations due to rash were reported.

*Liver enzyme elevation*
In SOHO-01 whole study 20 mg BID safety population, alanine aminotransferase (ALT) increase was reported in 14.6% of patients treated with Hyrnuo. Grade 3 ALT increase was observed in 1.4%, and Grade 4 ALT increase in 0.3%. Aspartate aminotransferase (AST) increase was reported in 14.6% of patients. Grade 3 AST increase was reported in 1.4% of patients. No grade 4 AST increase was reported.
The median time to first onset of ALT increase or AST increase was 1.4 months. Among patients with ALT increase, 2.8% had dose reduction, and 2.1% had a dose interruption. For those with AST increase, dose reduction occurred in 1.7%, and dose interruption in 1.4%. No drug discontinuations due to increased AST/ALT increased were reported.

*ILD/pneumonitis*

In SOHO-01 whole study 20 mg BID safety population, ILD/pneumonitis occurred in one patient (0.3%) treated with Hyrnuo (Grade 3). No Grade 4 ILD/pneumonitis was reported.

*Ocular toxicity*

In SOHO-01 whole study 20 mg BID safety population, ocular toxicity was reported in 7.7% of patients treated with Hyrnuo of whom 7.3% were dry eyes. Grade 1 was reported in 6.3% of patients, Grade 2 in 1.0%, and one (0.3%) Grade 3 case (corneal epithelial microcysts with temporary unilateral blindness).

*Pancreatic enzyme elevation*

In SOHO-01 whole study 20 mg BID safety population increased amylase was reported in 14.3% of patients treated with Hyrnuo, including 0.7% Grade 3 or 4. Increased lipase elevation occurred in 14.3% of patients treated with Hyrnuo, including 0.7% Grade 3 or 4. Increases in amylase or lipase were asymptomatic and not associated with pancreatitis.

The median time to onset of increased amylase/lipase was 0.69 months (range 0.2 to 20.4 months). Two patients (0.7%) required interruption of Hyrnuo due to increased lipase and 3 patients (1.0%) required interruption of Hyrnuo due to increased amylase. One patient (0.3%) required dose reduction due to increased amylase. No drug discontinuations due to pancreatic enzyme elevations were reported.

Elderly
Of the 287 patients in the SOHO-01 whole study 20 mg BID safety population 122 (42.5%) patients were 65 years or older. No overall differences in effectiveness were observed between these older and younger patients. Grade 3 or 4 diarrhoea was observed in 23.1% of patients aged ≥75 years and 14.1% of patients <75 years old.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store

### 4.9 Overdose

The highest dose of Hyrnuo studied clinically was 40 mg twice daily, equivalent to a total daily dose of 80 mg. At this dose, the dose-limiting adverse drug reactions observed were stomatitis, vomiting, and diarrhoea.

There is no specific antidote for Hyrnuo overdose.

In the event of an overdose, the patient should be closely monitored, and general supportive treatment should be considered based on signs and symptoms.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors. ATC code: L01EH0X

Mechanism of action
Sevabertinib is a reversible tyrosine kinase inhibitor (TKI) that potently targets mutant forms of HER2 (including exon 20 insertions and point mutations) as well as wildtype HER2.

*In vitro*, sevabertinib inhibited the phosphorylation of mutant HER2 and reduced downstream signalling. In cellular assays, sevabertinib inhibited growth of cultured tumour cells expressing mutant HER2 with $IC_{50}$ values <9 nM.

*In vivo*, sevabertinib demonstrated antitumour activity in subcutaneous mouse xenograft models derived from human lung tumours with *HER2* (*ERBB2*) mutations.

In addition, sevabertinib demonstrated activity on certain mutant forms of the epidermal growth factor receptor (EGFR). It exhibited weak cellular activity against wildtype EGFR.

Pharmacodynamic effects

Higher sevabertinib exposure, across the dose range of 10 to 80 mg total daily dose (0.25 times to 2 times the recommended dose), was associated with an increased probability of diarrhoea (including Grade 3) and rash.

Higher sevabertinib exposure, across the dose range of 10 mg twice daily (0.5 times the recommended dose) to 20 mg twice daily, was associated with greater reduction in tumour size.

No large changes in the mean QTcF interval (i.e., >20 ms) from baseline were detected in patients after oral administration of sevabertinib at doses up to 2 times the recommended total daily dose.

Clinical efficacy and safety

The efficacy and safety of Hyrnuo were evaluated in an open-label, single-arm, multicentre, multi-cohort clinical study (SOHO-01).

The study included adult patients with advanced NSCLC with activating *HER2* (*ERBB2*) mutations who had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. The primary efficacy population (Group D) included 81 patients who had received prior systemic therapy but were naïve to therapy targeting HER2 activating mutations. The supportive efficacy population (Group E) included 55 patients who had received prior systemic therapy and had documented progression to HER2-targeted ADCs.

Activating *HER2* (*ERBB2*) mutations were determined in tumour tissue or plasma by local laboratories prior to enrolment.

Patients with treated, stable and asymptomatic brain metastases were allowed. Patients with symptomatic CNS metastases, clinically significant cardiac disease, and history of steroid dependent ILD/pneumonitis were excluded from the study.

Patients received 20 mg Hyrnuo twice daily until disease progression or unacceptable toxicity.

The primary efficacy outcome measure was confirmed objective response rate (ORR) as assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Additional efficacy outcome measures included duration of response (DOR), disease control rate (DCR) and

progression-free survival (PFS) assessed by BICR using RECIST v1.1, as well as overall survival (OS).

*SOHO-01 Study Group D (primary efficacy population)*

Efficacy was evaluated in 70 patients with advanced non-squamous NSCLC with *HER2* (*ERBB2*) TKD activating mutations, based on prospective local testing, who had received prior systemic therapy and were naïve to therapy targeting HER2 activating mutations (Group D).

Baseline demographic and disease characteristics were: median age 59 years (range 29 to 77 years) and 67.1% female. The racial distribution included 70.0% Asian, 22.9% White, and 1.4% Black. Patients had an ECOG performance status of either 0 (38.6%) or 1 (61.4%); 68.6% were never-smokers, 28.6% were former smokers and 2.9% were current smokers. The majority of patients (91.4%) had stage IV disease and all patients had adenocarcinoma histology; 20.0% had stable brain metastases. The median number of prior therapies was 1 (range 1 to 8); 94.3% of patients received prior platinum-based chemotherapy, 71.4% received prior immunotherapy, and 68.6% received both in combination. Among the patients, 70% had an exon 20 Y772dupYVMA insertion.

The median treatment duration for Group D was 10.0 months (range 0 to 30 months), and the median duration of follow-up was 12.2 months (range 1 to 30 months) at the time of the data cut-off (28 March 2025).
SOHO-01 study Group D efficacy results for ORR and DOR are presented in Table 5.

**Table 5: Efficacy Results for SOHO-01 Study Group D**[a]

| **Efficacy Parameter** | **Group D**<br>**N=70** |
|---|---|
| **Confirmed Objective Response Rate (ORR)[b, c], n (%)**<br>**[95% CI]** | 50 (71.4%)<br>[59.4, 81.6] |
| Complete Response (CR), n (%) | 2 (2.9%) |
| Partial Response (PR), n (%) | 48 (68.6%) |
| **Duration of Response (DOR)[c]** | N=50 |
| Median, months[d] (95% CI) | 9.2 (6.3, 15.0) |
| Range, months | 1.3+, 25.7+ |
| DOR ≥ 6 months[e], n (%) | 27 (54.0%) |
| DOR ≥ 9 months[e], n (%) | 13 (26.0%) |
| DOR ≥ 12 months[e], n (%) | 9 (18.0%) |

CI – Confidence Interval; '+' – censored value

a Based on 28 March 2025 data cut.

b ORR 95% CI calculated using Clopper-Pearson method.

c Assessed by Blinded Independent Central Review (BICR).

d Kaplan-Meier estimate.

e Observed proportion of responding patients with duration of response beyond landmark time.

Stable disease was observed in 13 patients (18.6%). The Disease Control Rate (DCR) (calculated based on the proportion of patients with a confirmed best

overall response of CR, PR, or stable disease of at least 12 weeks following the first study treatment administration) was 84.3% (N=59) (95% CI: [73.6, 91.9]).

Consistent efficacy results in subgroups by prior therapy, presence of brain metastases, or age were observed in Group D.

*SOHO-01 Group E (supportive efficacy population)*

Efficacy was also evaluated in 52 patients with advanced non-squamous NSCLC with *HER2 (ERBB2)* TKD activating mutations, based on prospective local testing, who had received prior systemic therapy and progression to HER2-targeted ADCs (Group E).

Baseline demographic and disease characteristics from the 52 patients of the supportive efficacy population (Group E) were: median age 65 years (range 35 to 91 years) and 67.3% female. The racial distribution included 61.5% Asian, 26.9% White, and 5.8% Black. Patients had an ECOG performance status of either 0 (28.8%) or 1 (71.2%); 65.4% were never-smokers, and 34.6% were former smokers. The majority of patients (84.6%) had stage IV disease and all patients had adenocarcinoma histology; 28.8% had stable brain metastases. The median number of prior therapies was 2 (range 1 to 8); 76.9% of patients received prior platinum-based chemotherapy, 55.8% received prior immunotherapy, and 55.8% received both in combination. Among the patients,77% of patients had an exon 20 Y772dupYVMA insertion.

The median treatment duration for Group E was 5.7 months (range 0 to 19 months), and the median duration of follow-up was 10.9 months (range 2 to 20 months) at the time of the data cut-off (28 March 2025).

SOHO-01 study Group E efficacy results for ORR and DOR are presented in Table 6.

**Table 6: Efficacy results for SOHO-01 study Group E**[a]

| **Efficacy Parameter** | **Group E N=52** |
|---|---|
| **Confirmed Objective Response Rate (ORR)**[b, c], n (%)<br>[95% CI] | 20 (38.5%)<br>[25.3, 53.0] |
| Complete Response (CR), n (%) | 3 (5.8%) |
| Partial Response (PR), n (%) | 17 (32.7%) |
| **Duration of Response (DOR)**[c] | N=20 |
| Median, months[d] (95% CI) | 7.0 (5.6, NE) |
| Range, months | 1.0+, 17.2+ |
| DOR ≥ 6 months[e], n (%) | 12 (60.0%) |
| DOR ≥ 9 months[e], n (%) | 6 (30.0%) |
| DOR ≥ 12 months[e], n (%) | 2 (10.0%) |

CI – Confidence Interval; NE - not estimable; '+' – censored value

a Based on 28 March 2025 data cut.

b ORR 95% CI calculated using Clopper-Pearson method.

c Assessed by Blinded Independent Central Review (BICR).

[d] Kaplan-Meier estimate.
[e] Observed proportion of responding patients with duration of response beyond landmark time.

Stable disease was observed in 23 patients (44.2%). The Disease Control Rate (DCR) (calculated based on the proportion of patients with a confirmed best overall response of CR, PR, or stable disease of at least 12 weeks following the first study treatment administration) was 73.1% (N=38) (95% CI: [59.0, 84.4]).

Paediatric population
The MHRA has waived the obligation to submit the results of studies with Hyrnuo in all subsets of the paediatric population in the treatment of lung cancer (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The MHRA will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of sevabertinib have been characterised in patients with advanced NSCLC harbouring activating HER2 (ERBB2) or EGFR mutations and in healthy subjects.

Absorption
Sevabertinib reached maximum plasma concentrations ($C_{max}$) around 2 hours after oral administration of 20 mg twice daily under fed conditions in patients with advanced NSCLC.

Sevabertinib plasma concentrations reached steady-state within 3 days and the mean accumulation ratio after continuous 20 mg twice daily oral dosing under fed conditions was 1.65.

The geometric mean [coefficient of variation (CV%)] maximum plasma concentration ($C_{max}$) was 902 ng/mL (44.9%) and area under the plasma concentration-time curve from time 0 to 12 hours ($AUC_{0-12hr}$) was 6640 ng*h/mL (50.2%) at steady-state.
The mean AUC for sevabertinib was decreased by 27.6% when administered with a high-fat meal, and 16.1% when administered with a low-fat meal, compared to fasting. In clinical trials sevabertinib was administered with food.

Distribution
The geometric mean (CV%) apparent volume of distribution ($V_z/F$) is 28.1 L (42.2%).

Binding of sevabertinib to human plasma proteins *in vitro* was 95.3% and was independent of drug concentration within the clinically relevant dose range.

The blood-to-plasma concentration ratio was 0.61.

Biotransformation
Sevabertinib is metabolised primarily by oxidative metabolism mediated by CYP3A4 and to a minor extent by CYP1A1 as well as by glucuronidation mediated by UGT enzymes.

One major circulating plasma metabolite, M1, has been identified. M1 is highly protein bound (98.1%).

Based on preclinical data M1 is less potent on the *HER2* (*ERBB2*) mutations tested in antiproliferative assays compared to sevabertinib. Based on systemic exposure, relative potency, and pharmacokinetic properties, M1 is unlikely to significantly contribute to the clinical activity of sevabertinib

Elimination
The geometric mean elimination half-life for sevabertinib is approximately 5-6 hours in patients with advanced NSCLC. The mean elimination half-life for the metabolite M1 is approximately 10 hours in healthy volunteers.

The apparent clearance (CL/F) of sevabertinib following oral administration was 3.6 L/hour (CV: 55.2%).

Following oral administration of sevabertinib, 83.6% of the dose was excreted with faeces and less than 11% with urine (mainly as metabolites). Less than 2% of the dose was excreted unchanged in urine.

More than 81% of the dose was recovered within 3 days and 94.1% within 14 days after administration.

Linearity/non-linearity
Sevabertinib exposure increases dose-proportionally over the dose range from 10 to 80 mg total daily dose in patients with advanced NSCLC.

There is no clinically relevant change in sevabertinib pharmacokinetics with respect to time.

Special Populations
*Paediatric patients*
No studies have been conducted to investigate the pharmacokinetics of sevabertinib in children or adolescents below 18 years of age.

*Elderly*
Sevabertinib AUC in patients ≥65 years were similar to those in younger patients (<65 years).

*Patients with hepatic impairment*

Based on available clinical data and a population pharmacokinetic analysis in patients with advanced NSCLC, sevabertinib exposure was similar in patients with mild hepatic impairment (total bilirubin ≤ 1.5 × ULN and any AST) and normal hepatic function.

The pharmacokinetics of sevabertinib have not been studied in patients with moderate (total bilirubin >1.5 to ≤3 times ULN and any AST) or severe (total bilirubin >3x ULN and any AST) hepatic impairment (see section 4.2).

*Patients with renal impairment*
Based on available clinical data and a population pharmacokinetic analysis in patients with advanced NSCLC, sevabertinib exposures were similar in patients with mild (eGFR 60 to 89 mL/min) and moderate (eGFR 30 to 59 mL/min) renal impairment and normal renal function (eGFR ≥90 mL/min).

The pharmacokinetics of sevabertinib have not been studied in patients with severe renal impairment (eGFR <30 mL/min).

Other special populations
*Effect of gender, smoking status, race and body weight*
No clinically relevant differences in the pharmacokinetics of sevabertinib were observed based on gender, smoking status, ethnicity (White, Asian, or Black) and body weight.

## 5.3 Preclinical safety data

Systemic toxicity
In toxicology studies of up to 13 weeks in rats and cynomolgus monkeys, the main findings included reduced body weight and diarrhoea. These findings were observed at exposures corresponding to 0.8 times the human exposure (based on unbound AUC) at 20 mg twice daily. In the rat, histopathology revealed atrophic, inflammatory and/or degenerative processes in epithelial and mucosal tissues (gastrointestinal tissue, to a lesser extent skin). Atrophic, inflammatory and/or degenerative changes were also observed in the gastrointestinal mucosa in monkeys. Gastrointestinal and skin findings were largely reversible within 2 weeks of cessation of treatment.

Embryotoxicity / Teratogenicity
Disruption or depletion of HER2/EGFR in mouse models has shown that HER2/EGFR signalling is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-foetal/post-natal survival and development.

In pilot embryo-foetal development studies, pregnant rats received oral doses of sevabertinib up to 11 mg/kg/day during the period of organogenesis. Administration of sevabertinib resulted in maternal toxicity (body weight loss, reduced body weight gain, low food consumption, diarrhoea) at 7 mg/kg and 11 mg/kg corresponding to 0.5 to 1.1 times the human exposure (based on

unbound AUC) at 20 mg twice daily. Foetal effects included significantly reduced foetal and placenta weights, which resulted in reduced gravid uterine weights. No foetal malformations or variations were noted. The pivotal embryo-foetal development studies with pregnant rats revealed a reduction in foetal weights (combined and individual sexes) and a reduction in gravid uterine weight in the sevabertinib treated groups at doses between 1.5 and 6 mg/kg. No foetal malformations were noted.
Studies in rabbits were not conducted.

Following administration of radiolabelled sevabertinib to lactating rats, sevabertinib or its metabolites are excreted in milk. The radioactivity concentration in milk was 13 to 26-fold higher than that in the plasma and within a collection period of 32 hours approximately 1.3% of the administered dose of sevabertinib was excreted into the milk.

Reproduction toxicity
Specific studies on fertility have not been performed.

Genotoxicity and carcinogenicity
Carcinogenicity studies with sevabertinib have not been conducted.

Sevabertinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in either an *in vitro* micronucleus assay or an *in vivo* micronucleus assay in rats.

Safety pharmacology
Overall, non-clinical safety pharmacology studies reveal no special hazard for humans.

Sevabertinib had no adverse effects on hemodynamic parameters in dogs and on CNS and respiratory function in rats at exposures (unbound $C_{max}$ at steady state) at least 10 times the human exposures at 20 mg twice daily.

*In vitro*, sevabertinib inhibited the hERG potassium channel at clinically relevant unbound plasma concentrations. *In vivo*, in telemetered dogs, delayed cardiac ventricular repolarisation (QTc interval prolongation) was observed when sevabertinib was administered at approximately 12 times the human exposure at 20 mg twice daily (relative to unbound $C_{max}$ at steady state).

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone (E 1202)
Lactose monohydrate

Magnesium stearate (E 470b)

Film coat
Ferric oxide red (E 172)
Hypromellose 5 cP (E 464)
Macrogol 3350 (E 1521)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

PVC-PVDC/Aluminium blisters containing 28 film-coated tablets.

Each pack contains 112 (28x4) film-coated tablets.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading
RG2 6AD

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0764

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/04/2026

## 10 DATE OF REVISION OF THE TEXT

01/04/2026