Product Monograph

Including Patient Medication Information

^{Pr}HYRNUO™

Sevabertinib tablets

For oral use

10 mg sevabertinib

Protein kinase inhibitor

HYRNUO, indicated for:

- the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have *HER2 (ERBB2)* tyrosine kinase domain (TKD) activating mutations and who have received a prior systemic therapy

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for HYRNUO please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

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Date of Authorization:
2026-01-29

Control Number: 297051

What is a Notice of Compliance with Conditions (NOC/c)?

A NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

Recent Major Label Changes

Not applicable	

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

HYRNUO (sevabertinib) is indicated for:

- the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have *HER2 (ERBB2)* tyrosine kinase domain (TKD) activating mutations and who have received a prior systemic therapy.

  Marketing authorization with conditions was based on confirmed objective response rate (ORR) and duration of response (DOR) from one single-arm trial (see 14 Clinical Trials). An improvement in survival has not yet been established.

1.1. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of HYRNUO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients (see 7.1.4 Geriatrics).

2. Contraindications

- HYRNUO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4. Dosage and Administration

4.1. Dosing Considerations

- Confirm the presence of *HER2 (ERBB2)* TKD activating mutations in tumour specimens using a validated test prior to initiation of therapy with HYRNUO (see 10.1 Mechanism of Action).

4.2. Recommended Dose and Dosage Adjustment

The recommended dose of HYRNUO is 20 mg (two 10 mg tablets) taken orally twice daily until disease progression or unacceptable toxicity.

Pediatrics (< 18 years of age)

The safety and efficacy of HYRNUO in children and adolescents below 18 years of age have not been established (see 1.1 Pediatrics).

Geriatrics (≥ 65 years of age)

No dose adjustment is necessary in patients ≥ 65 years (see 10.3 Pharmacokinetics, Geriatrics).

Patients with Hepatic Impairment

Use in patients with moderate or severe hepatic impairment is not recommended. 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.

No dose adjustment is necessary for patients with mild hepatic impairment (total bilirubin ≤ 1.5 x ULN and any AST). No clinically relevant increase in sevabertinib exposure was observed in patients with mild hepatic impairment (see 10.3 Pharmacokinetics, Hepatic Insufficiency).

Patients with Renal Impairment

No dose adjustment is considered necessary in patients with mild or moderate renal impairment.

No clinically relevant increase in sevabertinib exposure was observed in patients with mild (estimated Glomerular Filtration Rate [eGFR] 60 to 89 mL/min) or moderate (eGFR 30 to 59 mL/min) renal impairment (see 10.3 Pharmacokinetics, Renal Insufficiency). The pharmacokinetics of sevabertinib have not been studied in patients with severe renal impairment (eGFR less than 30 mL/min).

Dose Modifications for Adverse Reactions

Management of adverse reactions may require temporary dose interruption, dose reduction, or discontinuation of HYRNUO based on individual safety and tolerability. 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 HYRNUO Dose Reductions 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 7 Warnings and Precautions and 8 Adverse Reactions).

Table 2 – Recommended HYRNUO Dose Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Recommended HYRNUO Dose Modification
Diarrhea	Intolerable Grade 2 or Grade 3	• Interrupt HYRNUO until recovery to Grade ≤1. • Resume HYRNUO at the same dose or the next lower dose. • For recurrence, resume HYRNUO at the next lower dose.
	Grade 4	• Permanently discontinue HYRNUO.

Adverse Reaction	Severity[a]	Recommended HYRNUO Dose Modification
Hepatotoxicity	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. • Resume HYRNUO at next lower dose.
	ALT or AST ≥3 x ULN *with* total bilirubin ≥2 x ULN or Grade 4 total bilirubin	• Permanently discontinue HYRNUO.
Interstitial lung disease (ILD)/pneumonitis	Any Grade	• Permanently discontinue HYRNUO.
Ocular toxicity	Grade 2	• Interrupt HYRNUO until recovery to Grade ≤1. • Resume HYRNUO at the next lower dose. • For recurrence, permanently discontinue HYRNUO.
	Grade 3 or Grade 4	• Permanently discontinue HYRNUO.
Pancreatic Enzyme Elevation	Grade 3	• Interrupt HYRNUO until recovery to Grade ≤2 or baseline. • Resume HYRNUO at the next lower dose.
	Grade 4	• Permanently discontinue HYRNUO.
Other adverse reactions	Intolerable or recurrent Grade 2 or Grade 3	• Interrupt HYRNUO until recovery to Grade ≤1. • Resume HYRNUO at the same dose or at the next lower dose. • For recurrence, resume HYRNUO at the next lower dose.

Adverse Reaction	Severity[a]	Recommended HYRNUO Dose Modification
	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 for 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 9.4 Drug-Drug Interactions). For patients taking a current total daily dose of 10 mg (one 10 mg tablet once daily), 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	Reduced HYRNUO Dosage
Two 10 mg tablets twice daily (total daily dose of 40 mg)	One 10 mg tablet twice daily (total daily dose of 20 mg)
One 10 mg tablet twice daily (total daily dose of 20 mg)	One 10 mg tablet once daily (total daily dose of 10 mg)
One 10 mg tablet once daily (total daily dose of 10 mg)	Withhold HYRNUO

4.4. Administration

HYRNUO is 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.

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

4.5. 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. The patient should not take two doses at the same time to make up for the missed dose.

5. Overdose

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.

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 diarrhea.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 4 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
oral	tablet, 10 mg	Cellulose microcrystalline, crospovidone, ferric oxide red, hypromellose 5 cP, lactose monohydrate, macrogol 3350, magnesium stearate

Description

Each tablet contains 10 mg of sevabertinib.

HYRNUO 10 mg tablets are supplied as red brown film-coated, round, biconvex tablets debossed with "SE" on one side and "10" on the other side.

HYRNUO 10 mg tablets are supplied in bottles of 120 tablets closed with a child-resistant screw cap.

7. Warnings and Precautions

Driving and Operating Machinery

There is no evidence that HYRNUO will affect the ability to drive or use machines.

Gastrointestinal

Diarrhea

Diarrhea has been reported during treatment with HYRNUO and can be severe, leading to dehydration and electrolyte imbalance if untreated.

In the pooled safety population (see 8.1 Adverse Reaction Overview), based on adverse reaction data, diarrhea was reported in 84.3% of patients who received HYRNUO including Grade 3 diarrhea in 14.2%. The median time to first onset of any grade diarrhea was 4 days. Dosage interruptions were required in 15.3% of patients, and dose reductions occurred in 11.6% of patients receiving HYRNUO.

Patients should be advised to start an antidiarrheal agent (e.g. loperamide), and to increase fluid and electrolyte intake at first sign of diarrhea or increased bowel movement frequency. Based on the

severity of the diarrhea, patients may require temporary interruption, dose reduction or permanent discontinuation of therapy with HYRNUO (see 4.2 Recommended Dose and Dosage Adjustment, Dose Modifications for Adverse Reactions).

Hepatic/Biliary/Pancreatic

Hepatotoxicity

HYRNUO can cause hepatotoxicity, as evidenced by worsening treatment-emergent hepatic function laboratory values.

In the pooled safety population (see 8.1 Adverse Reaction Overview), based on adverse reaction data, 12.7% of patients treated with HYRNUO experienced increased alanine aminotransferase (ALT), including 1.5% Grade 3. Increased aspartate aminotransferase (AST) occurred in 12.3% of patients, including 1.1% Grade 3.

Based on laboratory data, 34.7% of patients in the pooled safety population experienced increased ALT, including 2.3% Grade 3. Increased AST occurred in 35.5% of patients treated with HYRNUO, including 2.3% Grade 3. Increased bilirubin occurred in 11.7% of patients treated with HYRNUO. The median time to first onset of AST or ALT elevation was 1.4 (range 0.2 to 14.5) months.

HYRNUO was interrupted due to hepatic functional abnormality (1.1%), increased ALT (2.2%), and increased AST (1.5%). Permanent discontinuation due to hepatic function abnormality occurred in 0.4% of patients.

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. Interrupt, reduce the dose, or permanently discontinue HYRNUO based on the severity of the adverse reaction (see 4.2 Recommended Dose and Dosage Adjustment).

Pancreatic Enzyme Elevation

HYRNUO can cause elevations in amylase and lipase levels.

In the pooled safety population (see 8.1 Adverse Reaction Overview), based on laboratory data, increased amylase occurred in 31.7% of patients treated with HYRNUO, including 3.1% Grade 3 or 4. Increased lipase occurred in 39.9% of patients treated with HYRNUO, including 9.9% Grade 3 or 4. The median time-to-onset of Grade 3 or higher increased amylase/lipase was 1.4 (range 0.2 to 17) months.

One patient (0.4%) required interruption of HYRNUO due to increased lipase and 3 (1.1%) required interruption due to increased amylase.

Monitor amylase and lipase regularly during treatment with HYRNUO. Interrupt, reduce the dose, or permanently discontinue HYRNUO based on the severity of the adverse reaction (see 4.2 Recommended Dose and Dosage Adjustment).

Ophthalmologic

Ocular Toxicity

HYRNUO can cause ocular toxicity.

In the pooled safety population (see 8.1 Adverse Reaction Overview), ocular toxicity occurred in 8.6% of patients treated with HYRNUO. Overall, most cases observed were Grade 1 (7.1%) and Grade 2 (1.1%). One patient (0.4%) experienced Grade 3 corneal epithelial microcysts with temporary loss of vision in one eye.

Promptly refer patients presenting with new or worsening eye symptoms to an ophthalmologist. Interrupt, reduce the dose or permanently discontinue HYRNUO based on the severity of the adverse reaction (see 4.2 Recommended Dose and Dosage Adjustment).

Reproductive Health

Female patients of childbearing potential or male patients with partners of childbearing potential must be informed that HYRNUO may cause fetal harm (see 7.1.1 Pregnancy and 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

The pregnancy status of patients of childbearing potential should be verified prior to initiation of HYRNUO.

Patients 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 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 partner, a condom is required during and for 1 week after completion of treatment with HYRNUO. Exposure of the fetus to sevabertinib through seminal transfer to the pregnant partner must be avoided, as this could affect development of the fetus.

- **Fertility**

There is no human data on the effect of HYRNUO on fertility (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

Respiratory

Interstitial Lung Disease/Pneumonitis

HYRNUO may cause severe interstitial lung disease (ILD)/pneumonitis.

In the pooled safety population (see 8.1 Adverse Reaction Overview), ILD/pneumonitis occurred in 1 patient (0.4%) treated with HYRNUO (Grade 3).

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g. dyspnea, cough, fever). Discontinue HYRNUO upon confirmation of ILD/pneumonitis (see 4.2 Recommended Dose and Dosage Adjustment).

7.1. Special Populations

7.1.1. Pregnancy

There is no data available on the use of HYRNUO in pregnant patients.

Available animal studies do not provide sufficient information regarding reproductive toxicity (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

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

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

HYRNUO should not be given during pregnancy unless the benefit of treatment to the patient is considered to outweigh potential risks to the fetus.

Patients taking HYRNUO during pregnancy or who become pregnant while taking HYRNUO should be advised of the potential hazard to the fetus.

7.1.2. Breastfeeding

There is no data on the presence of sevabertinib or its metabolites in human milk.

In rats, sevabertinib or its metabolites are excreted in milk (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

A risk to the breastfed child cannot be excluded. Breastfeeding should be discontinued during treatment with HYRNUO and for 1 week following the final dose.

7.1.3. Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of HYRNUO in children and adolescents below 18 years of age have not been established.

7.1.4. Geriatrics

Geriatrics (≥ 65 years of age): Of the 81 patients in the SOHO-01 clinical study Group D, 26 (32.1%) patients were 65 years and over. Clinical studies of HYRNUO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The safety of HYRNUO was evaluated in an open-label, single-arm, multicenter, multi-cohort clinical study (SOHO-01). The primary safety analysis population (Group D) included 81 patients with locally advanced or metastatic *HER2*-mutated NSCLC who had received prior systemic therapy but were naïve to therapy targeting *HER2* mutations. Supportive safety data was derived from Group E, which included 55 patients with *HER2*-mutated NSCLC who had received prior systemic therapy and had documented progression on HER2-targeted antibody-drug conjugates (ADCs). Patients in Groups D and E were treated with HYRNUO 20 mg twice daily until disease progression or unacceptable toxicity.

The pooled safety population referred to in 7 Warnings and Precautions reflects exposure to at least one dose of HYRNUO 20 mg orally twice daily in 268 treatment-naïve or previously treated patients with locally advanced or metastatic NSCLC harboring *HER2* and/or *EGFR* mutations. Among the 268 patients who received HYRNUO, 35% were exposed for greater than 6 months and 12% were exposed for greater than one year.

In Group D, the median age of patients who received HYRNUO was 60 years (range: 29-82) and 62% were female. The majority of patients were Asian (70%), followed by White (22%), and Black (1.2%).

All patients in Group D experienced at least one adverse event (AE). Adverse drug reactions (considered by the investigator to be related to HYRNUO) occurred in 96.3% of patients. The most common adverse reactions (>20%) in patients receiving HYRNUO were diarrhea (84.0%), rash (71.6%), and paronychia (30.9%). The most common (>2%) Grade 3 or 4 laboratory abnormalities were lipase increased (12.8%),

hypokalemia (10.0%), lymphocyte count decreased (6.6%), aspartate aminotransferase (AST) increased (5.0%), and alanine aminotransferase (ALT) increased (5.0%).

Serious adverse reactions occurred in 13.6% of patients in Group D. Serous adverse reactions reported in ≥2 patients included diarrhea (6.2%), nausea (2.5%), and hepatic function abnormal (2.5%).

Fatal AEs occurred in 6 patients (7.4%) in Group D with a primary cause of progressive disease (6.2%). None of these deaths were assessed by the investigator as study drug-related.

Permanent discontinuation due to adverse reactions occurred in 4 patients (4.9%) in Group D. Adverse reactions leading to permanent discontinuation of HYRNUO were corneal epithelial microcysts (1.2%), hepatic function abnormal (1.2%), electrocardiogram QT prolonged (1.2%), and dyspnea (1.2%).

Dose interruptions due to adverse reactions occurred in 30.9% of patients who received HYRNUO. The most frequent (>3%) adverse reactions leading to dose interruption were diarrhea (16.0%), hypokalemia (4.9%), and nausea (3.7%).

Dose reductions due to adverse reactions occurred in 23.5% of patients who received HYRNUO. The most frequent (>2%) adverse reactions leading to dose reduction were diarrhea (11.1%), ALT increased (2.5%), hepatic function abnormal (2.5%), and AST increased (2.5%).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect the frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Non-Small Cell Lung Cancer (NSCLC)

Adverse reactions, considered related to HYRNUO by the investigator, reported in the SOHO-01 clinical study Group D (N = 81) are listed in Table 5. Among these patients, 60% were exposed to greater than 6 months of HYRNUO and 20% were exposed to greater than 1 year.

Table 5 – Adverse Reactions (≥10%) in Patients from SOHO-01 (Group D)

System Organ Class (MedDRA)[a]	HYRNUO (N=81)	
	All Grades n (%)	Grade 3 or Grade 4[b] n (%)
Blood and lymphatic system disorders		
Anemia	11 (13.6%)	1 (1.2%)
Gastrointestinal disorders		
Diarrhea	68 (84.0%)	19 (23.5%)
Stomatitis[c]	26 (32.1%)	1 (1.2%)
Nausea	15 (18.5%)	2 (2.5%)
Vomiting	13 (16.0%)	3 (3.7%)
Investigations		
Weight decreased	14 (17.3%)	0
Aspartate aminotransferase increased	13 (16.0%)	1 (1.2%)
Alanine aminotransferase increased	12 (14.8%)	1 (1.2%)

System Organ Class (MedDRA)[a]	HYRNUO (N=81)	
	All Grades n (%)	Grade 3 or Grade 4[b] n (%)
Amylase increased	12 (14.8%)	0
Metabolism and nutrition disorders		
Hypokalemia	13 (16.0%)	4 (4.9%)
Decreased appetite	12 (14.8%)	3 (3.7%)
Skin and subcutaneous tissue		
Rash[d]	58 (71.6%)	0
Paronychia[e]	25 (30.9%)	0
Dry skin[f]	16 (19.8%)	0
Pruritis	13 (16.0%)	2 (2.5%)

a. Graded per NCI CTCAE version 5
b. No Grade 4 adverse reactions were reported
c. Stomatitis includes cheilitis, mouth ulceration, mucosal inflammation, stomatitis
d. Rash includes acne, acne varioliformis, dermatitis acneiform, eczema, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, skin exfoliation
e. Paronychia includes nail disorder, onycholysis, paronychia
f. Dry skin includes dry skin, xeroderma

Additional Information in Selected Adverse Reactions

Rash

In SOHO-01 (Group D), drug-related rash (grouped term) was reported in 71.6% of patients treated with HYRNUO and was mild to moderate in severity (Grade 1: 56.8% and Grade 2: 14.8%). No Grade 3 or 4 rash was reported. No dose interruption, dose reduction or treatment discontinuations due to rash were reported.

SOHO-01 (Group E)

The safety of HYRNUO was evaluated in 55 patients with advanced NSCLC harboring activating *HER2 (ERBB2)* mutations who had received prior systemic therapy, had documented progression to HER2-targeted antibody drug conjugates (ADCs) and who had received HYRNUO at 20 mg twice daily (Group E). The overall safety profile of Group E was comparable with that described above for Group D.

8.3. Less Common Clinical Trial Adverse Reactions

Clinically relevant adverse reactions in < 10% of patients who received HYRNUO in SOHO-01 (Group D) included:

- Cardiac disorders: cardiac arrhythmia[a]
- Eye disorders: ocular toxicity[b]
- Gastrointestinal disorders: abdominal pain[c]
- General disorders and Administration site conditions: fatigue[d]
- Investigations: lipase increased, blood creatinine increased
- Skin and subcutaneous tissue disorders: alopecia, palmar-plantar erythrodysesthesia syndrome

a. Cardiac arrhythmia includes arrhythmia, atrioventricular block complete, electrocardiogram QT prolonged, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia.
b. Ocular toxicity includes corneal epithelial microcysts, dry eye, ocular toxicity, visual acuity reduced, xerophthalmia
c. Abdominal pain includes abdominal distension, abdominal pain, abdominal pain upper
d. Fatigue includes asthenia, fatigue

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 6 summarizes the laboratory test abnormalities observed in SOHO-01 (Group D).

Table 6 – Laboratory Abnormalities that Worsened from Baseline in SOHO-01 (Group D)

Laboratory Parameter (in % of samples investigated)	**HYRNUO SOHO-01 Group D N=81[a], n (%)**	
	All Grades[b]	Grade 3 or Grade 4
Hematology		
Anemia	37 (46.3%)	1 (1.3%)
Lymphocyte count decreased	19 (31.1%)	4 (6.6%)
White blood cell decreased	17 (21.5%)	1 (1.3%)
Chemistry		
Lipase increased	40 (51.3%)	10 (12.8%)
Aspartate aminotransferase increased	37 (46.3%)	4 (5.0%)
Alanine aminotransferase increased	33 (41.3%)	4 (5.0%)
Hypokalemia	33 (41.3%)	8 (10.0%)
Hypomagnesemia	33 (41.3%)	0
Hypoalbuminemia	26 (32.5%)	2 (2.5%)
Hyperglycemia[c]	25 (32.5%)	1 (1.3%)
Creatinine increased	26 (32.5%)	0
Serum amylase increased	25 (32.1%)	1 (1.3%)
Hypocalcemia	23 (28.8%)	1 (1.3%)
Alkaline phosphatase increased	21 (26.3%)	0

Laboratory Parameter (in % of samples investigated)	HYRNUO SOHO-01 Group D N=81[a], n (%)	
	All Grades[b]	Grade 3 or Grade 4
Hyponatremia	21 (26.3%)	0
Hypertriglyceridemia	20 (25.0%)	0
Blood bilirubin increased	10 (12.5%)	0

a. The denominator used to calculate the rate varied from 61 to 80 based on the number of patients with a baseline value and at least one post-treatment value.
b. Graded per NCI CTCAE version 5 using only numeric values.
c. Graded per NCI CTCAE version 4.03 using only numeric values.

9. Drug Interactions

9.3. Drug-Behaviour Interactions

The interaction of HYRNUO with individual behavioural risks (e.g. cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

The drugs listed in Table 7 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 7 - Established or Potential Drug-Drug Interactions

Co-administered drug	Source of evidence	Effect	Clinical comment
Effects of other medicinal products on sevabertinib			
Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, ketoconazole, cobicistat, lopinavir/ritonavir, saquinavir/ritonavir	CT	Co-administration of multiple daily doses of itraconazole (200 mg), and sevabertinib (10 mg) increased sevabertinib exposure with a mean AUC ratio of 2.3 and a mean C_{max} ratio of 1.6 compared with administration of sevabertinib alone.	Concomitant use of strong CYP3A4 inhibitors during treatment with HYRNUO is not recommended. If concomitant use cannot be avoided, the HYRNUO dose should be modified as recommended (see 4.2 Recommended Dose and Dosage Adjustment, Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors).
Moderate CYP3A4 inhibitors (e.g. erythromycin)	C	Sevabertinib exposure may be increased when co-administered with moderate CYP3A4 inhibitors. Limited clinical data are available on the impact of concomitant use	It is recommended to closely monitor patients for adverse reactions.

Co-administered drug	Source of evidence	Effect	Clinical comment
		of moderate CYP3A4 inhibitors on sevabertinib plasma concentrations.	
Weak CYP3A4 inhibitors (e.g. fosaprepitant)	popPK	Based on a population pharmacokinetics analysis, no impact of concomitant use of weak CYP3A4 (and P-gp) inhibitors was found.	HYRNUO may be given concomitantly with weak CYP3A4 inhibitors without a clinically relevant drug-drug interaction.
Strong CYP3A4 (and P-gp) inducers (e.g. carbamazepine, phenytoin, rifabutin, rifampicin)	CT	Co-administration of multiple doses of carbamazepine (600 mg), and sevabertinib (40 mg), resulted in a decrease of 79% in mean AUC and a decrease of 57% in C_{max} of sevabertinib.	Use of strong CYP3A4 inducers 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.
P-gp and BCRP inhibitors (e.g. danicopan)	T	*In vitro*, sevabertinib is a substrate of P-glycoprotein (P-gp), and Breast Cancer Resistance Protein (BCRP). No clinically relevant interaction with P-gp or BCRP inhibitors is expected due to high permeability and limited unchanged excretion of sevabertinib.	If HYRNUO is given concomitantly with P-gp or BCRP inhibitors, a clinically relevant drug-drug interaction is not expected.
Proton pump inhibitors (PPI), H2-receptor antagonists, and locally acting antacids (e.g. esomeprazole)	CT	Co-administration of esomeprazole (40 mg), and sevabertinib (20 mg), under low-fat, low-calorie fed conditions demonstrated no clinically relevant effect on the exposure of sevabertinib (decrease of 10% in mean AUC).	HYRNUO may be given concomitantly with acid-reducing agents.
Effects of sevabertinib on other medicinal products			
Substrates of CYP3A4 (e.g. midazolam, alfentanil, cyclosporine,	CT	Sevabertinib is a weak inhibitor of CYP3A4. Co-administration of multiple daily doses of sevabertinib (20 mg twice	The related recommendation in the product information of sensitive CYP3A4 substrates with a narrow therapeutic window should be followed when co-administered with HYRNUO.

Co-administered drug	Source of evidence	Effect	Clinical comment
dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus)		daily) and midazolam, increased midazolam exposure with a mean AUC ratio of 1.95 and a mean C_{max} ratio of 1.8 compared with administration of midazolam alone. Concomitant use of HYRNUO may increase the plasma concentrations of sensitive CYP3A4 substrates.	
Substrates of CYP1A1 (e.g. riociguat, granisetron)	T	*In vitro*, sevabertinib is a strong inhibitor of CYP1A1 at clinically relevant concentrations. Co-administration of HYRNUO may increase the plasma concentrations of CYP1A1 substrates.	The related recommendation in the product information of these substrates should be followed when co-administered with HYRNUO.
Substrates of P-gp (e.g. dabigatran etexilate, digoxin)	CT	Sevabertinib is an inhibitor of P-gp. Co-administration of multiple daily doses of sevabertinib (20 mg twice daily) and dabigatran etexilate, increased dabigatran exposure with a mean AUC ratio of 1.4 while C_{max} was unchanged compared with administration of dabigatran etexilate alone. Concomitant use of HYRNUO may increase the plasma concentrations of sensitive P-gp substrates.	The related recommendation in the product information of sensitive P-gp substrates with a narrow therapeutic window should be followed when co-administered with HYRNUO.
Substrates of BCRP (e.g. rosuvastatin, methotrexate, atorvastatin)	CT	Sevabertinib is an inhibitor of BCRP. Co-administration of multiple daily doses of sevabertinib (20 mg twice daily) and rosuvastatin, increased rosuvastatin	The related recommendation in the product information of sensitive BCRP substrates should be followed when co-administered with HYRNUO.

Co-administered drug	Source of evidence	Effect	Clinical comment
		exposure with a mean AUC ratio of 1.3 and a mean C_{max} ratio of 1.4 compared with administration of rosuvastatin alone. Concomitant use of HYRNUO may increase the plasma concentrations of sensitive BCRP substrates.	
Substrates of MATE1 and MATE2-K) (e.g. metformin, cisplatin)	T	*In vitro*, sevabertinib is an inhibitor of Multidrug and Toxin Extrusion (MATE) 1 and 2-K at clinically relevant concentrations. Co-administration of HYRNUO may affect renal clearance of substrates of these transporters.	The related recommendation in the product information of these substrates should be followed when co-administered with HYRNUO.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; popPK = Population pharmacokinetic modeling

9.5. Drug-Food Interactions

Although a significant drug-food interaction has not been observed, for safety/tolerability reasons, this drug should be taken with food as recommended in 4.4 Administration. Avoid grapefruit or grapefruit juice as these may also increase plasma concentrations of sevabertinib.

9.6. Drug-Herb Interactions

Avoid hypericum perforatum (a CYP3A4 inducer), also known as St. John's wort, as it may decrease plasma concentrations of sevabertinib.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Sevabertinib is a tyrosine kinase inhibitor of human epidermal growth factor receptor 2 (HER2) and mutant epidermal growth factor receptor (EGFR).

In vitro, sevabertinib inhibited the phosphorylation of HER2 and mutant EGFR, and reduced downstream signaling. In cellular assays, sevabertinib inhibited proliferation of tumour cells overexpressing wild type or harboring *HER2* mutations.

In vivo, sevabertinib demonstrated anti-tumour activity in subcutaneous mouse xenograft models derived from human NSCLC tumours with an activating *HER2* exon 20 YVMA mutation.

10.2. Pharmacodynamics

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

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.

10.3. Pharmacokinetics

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

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

Table 8 - Summary of 20 mg Single Dose Pharmacokinetic Parameters in Patients with Advanced NSCLC Harboring Activating *HER2 (ERBB2)* or *EGFR* Mutations

	C_{max} (mcg/L) GeoMean (range)	**T_{max} (h)** Median (range)	**$t_{½}$ (h)** GeoMean (range)	**AUC_{0-12} (mcg*h/L)** GeoMean (range)	**CL/F (L/h)** GeoMean (range)	**Vz/F (L)** GeoMean (range)
20 mg twice daily	718 (159-2110)	2.02 (0.500-8.15)	5.48 (2.59-8.96)	4250 (1100-16600)	3.56 (0.944-12.5)	28.1 (12.2-99.4)

AUC = area under the curve; C_{max} = maximum drug concentration in plasma after dose; CL/F = apparent plasma clearance of drug; GeoMean = geometric mean; T½ = half life; T_{max} = time to reach C_{max}; Vz/F = apparent volume of distribution

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.

Food effect

In healthy volunteers, administration of sevabertinib (20 mg) after a low-fat, low-calorie or high-fat, high calorie meal decreased AUC_I by approximately 16.1% or 27.6% and C_{max} by 27.8% or 55.7%, respectively, compared with fasted conditions. T_{max} was delayed from about 1 h to 2 h (low-fat) or 4 h (high-fat). In clinical trials sevabertinib was administered with food.

Distribution

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

Binding of sevabertinib to human plasma proteins *in vitro* was 95.3%.

The blood-to-plasma concentration ratio was 0.61.

Metabolism

Sevabertinib is metabolized primarily by oxidative metabolism mediated by CYP3A4 and to a minor extent by CYP1A1 and glucuronidation mediated by UGT enzymes.

Elimination

The geometric mean elimination half-life for sevabertinib is approximately 5-6 hours in patients with advanced NSCLC.

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 feces and less than 11% with urine (mainly as metabolites). Less than 2% of the dose was excreted unchanged in urine.

Special populations and conditions

- Pediatrics

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

- Geriatrics

Sevabertinib AUC in patients ≥65 years was similar to those in younger patients (<65 years).

- Sex

No clinically relevant differences in the pharmacokinetics of sevabertinib were observed based on gender.

- Ethnic Origin

No clinically relevant differences in the pharmacokinetics of sevabertinib were observed based on ethnicity (White, Asian, or Black).

- Hepatic Insufficiency

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 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment).

- Renal Insufficiency

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).

11. Storage, Stability and Disposal

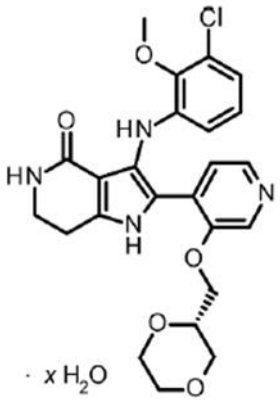
Store between 15°C to 30°C.

Keep out of reach and sight of children.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance(s):	sevabertinib
Chemical name:	3-(3-chloro-2-methoxyanilino)-2-{3-[(2S)-1,4-dioxan-2-ylmethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one hydrate
Molecular formula and molecular mass:	$C_{24}H_{25}ClN_4O_5$ (anhydrate) 484.93 g/mol (anhydrate)
Structural formula:	
Physicochemical properties:	The drug substance is a white to off-white to yellow to pinkish powder, isolated as a non-stoichiometric hydrate form of sevabertinib. It is slightly soluble in aqueous solution at pH 2, and practically insoluble in aqueous solutions at pH 4.5 and above.

14. Clinical Trials

14.1. Clinical Trials by Indication

Non-Small Cell Lung Cancer (NSCLC)

Table 9 - Summary of Patient Demographics for Clinical Trials in NSCLC; *HER2* (*ERBB2*) TKD Activating Mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects[a] (n)	Median age (range)	Sex (female/male)
SOHO-01[b] (Study 21607)	Phase 1/2 non-randomized, open-label, single-arm, multicenter multi-cohort	20 mg HYRNUO orally twice daily until disease progression or unacceptable toxicity	Group D: n = 73 Group E: n = 52	Group D: 59 years (29, 77) Group E: 65 years (35, 91)	Group D: 47/26 Group E: 35/17

a. *HER2 (ERBB2)* TKD Activating Mutations
b. Data cutoff as of 14 OCT 2024

The efficacy and safety of HYRNUO (sevabertinib) were evaluated in an open-label, single-arm, multicenter, 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 antibody drug conjugates (ADCs). Efficacy was evaluated in 73 patients in Group D and 52 patients in Group E with *HER2* (*ERBB2*) TKD activating mutations.

Activating *HER2 (ERBB2)* mutations were determined in tumour tissue or plasma by local laboratories prior to enrollment. Patients with treated, stable and asymptomatic brain metastases were eligible. Patients with symptomatic CNS metastases, clinically significant cardiac disease, and history of steroid dependent interstitial lung disease (ILD)/pneumonitis were excluded from the study.

Baseline demographic and disease characteristics from Group D patients with *HER2 (ERBB2)* TKD activating mutations were: median age 59 years (range 29 to 77 years) and 64% female. The racial distribution included 70% Asian, 23% White, 1.4% Black and 5.5% not reported. Patients had an ECOG performance status of either 0 (37%) or 1 (63%); 65.8% were never-smokers, 30.1% were former smokers and 4.1% were current smokers. The majority of patients (90.4%) had stage IV disease, 95.9% had adenocarcinoma histology; 19.2% had stable brain metastases. The median number of prior therapies was 1 (range 1 to 8); 94.5% of patients received prior platinum-based chemotherapy, 72.6% received prior immunotherapy, and 69.9% received both in combination. 67.1% of patients had a Y772_A775dup (YVMA) exon 20 insertion.

The major efficacy outcomes were confirmed objective response rate (ORR) and duration of response (DOR) as assessed by Blinded Independent Central Review (BICR) using RECIST v1.1. A lower boundary of 30% for ORR, considered to be clinically meaningful, was predefined as statistically significant for response. The ORR was defined as the proportion of patients with the best overall response of confirmed complete response (CR) or confirmed partial response (PR).

SOHO-01 Group D (primary efficacy population)

Efficacy results from SOHO-01 study Group D are presented in Table 10.

Table 10 – Efficacy Results for SOHO-01 Study Group D[a], Patients with *HER2* (*ERBB2*) TKD Activating Mutations

Efficacy Parameter	Group D N=73
Confirmed Objective Response Rate (ORR)[b,c] (95% CI)	65.8% (53.7%, 76.5%)
Complete Response (CR)	1.4%
Partial Response (PR)	64.4%
Duration of Response (DOR)[c]	**N=48**
Median, months[d] (95% CI)	6.8 (5.2, NE)
DOR ≥ 6 months[e]	27.1%

CI = Confidence Interval; NE = Not estimable

a. Based on 14 October 2024 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.

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 82.2% (95% CI: 71.5%, 90.2%). Consistent efficacy results were observed in pre-defined subgroups for Group D, including prior therapy, presence of brain metastases, and age.

16. Non-Clinical Toxicology

General toxicology

Sevabertinib was evaluated in repeat-dose toxicology studies in rats and cynomolgus monkeys, revealing dose-dependent adverse effects primarily affecting the gastrointestinal tract, epithelial and mucosal tissues, and thymus, with additional liver changes observed in female monkeys. In toxicology studies of up to 13 weeks in rats and cynomolgus monkeys, the main findings included reduced body weight and diarrhea. These findings were observed at exposures corresponding to >0.4 times the human exposure (based on total 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. Thymic atrophy in male and female monkeys and fat accumulation in the liver of female monkeys was observed at exposures corresponding to >0.10 times the human exposure (based on AUC at 20 mg twice daily).

Genotoxicity

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.

Carcinogenicity

Carcinogenicity studies with sevabertinib have not been conducted.

Reproductive and developmental toxicology

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

In embryo-fetal development studies, pregnant rats received oral doses of sevabertinib during the period of organogenesis from gestation to day 6 to 17. Sevabertinib caused maternal toxicity body weight loss, reduced body weight gain, low food consumption, and diarrhea at dosage of ≥7 mg/kg/day corresponding to 0.22 times the human exposure (based on AUC at 20 mg twice daily). Fetal effects included significantly reduced fetal and placenta weights, which resulted in reduced gravid uterine weights. The pivotal embryo-fetal development studies with pregnant rats revealed a reduction in fetal weights (combined and individual sexes) and a reduction in gravid uterine weight at dosage ≥6 mg/kg/day (0.2 times the human exposure based on AUC at the clinical dose).

In a human-induced pluripotent stem cell-based assay, sevabertinib demonstrated teratogenic potential by causing concentration dependent decrease in cardiomyocyte and hepatocyte differentiation markers.

Following administration of radiolabeled sevabertinib to lactating rats, sevabertinib or its metabolites are excreted in milk. Sevabertinib concentrations were 13 to 26 times higher in milk than in plasma. Approximately 1.3% of the administered dose of sevabertinib was excreted into the milk.

Specific studies on fertility have not been performed.

Special toxicology

In vitro, sevabertinib inhibited the hERG potassium channel at clinically relevant unbound plasma concentrations. *In vivo*, in telemetered dogs, delayed cardiac ventricular repolarization (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).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]HYRNUO™

sevabertinib tablets

This Patient Medication Information is written for the person who will be taking **HYRNUO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **HYRNUO**, talk to a healthcare professional.

What HYRNUO is used for:

For the following indication HYRNUO has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- HYRNUO is used to treat adults with a type of lung cancer called "non-small cell lung cancer" (NSCLC) when:
    - the cancer has a mutation (a change) in a gene named "*HER2*" (human epidermal growth factor)
    - the cancer has spread to other parts of your body
    - the cancer cannot be removed through surgery
    - you have tried another treatment for your cancer

Your healthcare professional will do a test to make sure that HYRNUO is the right treatment for you.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How HYRNUO works:

HYRNUO belongs to a group of cancer medicines called "protein kinase inhibitors."

The HER2 protein is a protein kinase and is found on the surface of some cells in the body. It is made in the body by the *HER2* gene which helps control how normal cells grow and divide.

A change in the *HER2* gene can make the body produce an abnormal HER2 protein. This can cause cells to grow without control and lead to cancer.

HYRNUO stops the abnormal protein from working and may slow down or stop the growth of the cancer. It may also help to shrink the cancer.

The ingredients in HYRNUO are:

Medicinal ingredient(s): sevabertinib

Non-medicinal ingredients: cellulose microcrystalline, crospovidone, ferric oxide red, hypromellose 5 cP, lactose monohydrate, macrogol 3350, and magnesium stearate

HYRNUO comes in the following dosage form(s):

Tablet: 10 mg

Do not use HYRNUO if:

- you are allergic to sevabertinib, any of the other ingredients of this medicine or any parts of the container (see **The ingredients in HYRNUO are**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take HYRNUO. Talk about health conditions or problems you may have including if you:

- have recurring diarrhea.
- have liver problems.
- have lung or breathing problems other than lung cancer.
- are pregnant, planning to become pregnant, or planning to have a child with your partner.
- are breastfeeding or plan to breastfeed.

Other warnings you should know about:

Diarrhea

HYRNUO can cause diarrhea during treatment. Diarrhea is when you have loose stools which can cause your body to lose water, important minerals and become dehydrated.

Talk to your healthcare professional before you take this medicine. You should have medicine available to treat diarrhea before you start taking HYRNUO.

If you get diarrhea while taking HYRNUO, tell your healthcare professional immediately. Drink fluids and take the medicine to treat your diarrhea as soon as possible. It is important the diarrhea is treated quickly.

Your healthcare professional may decide to lower the dose, pause or stop treatment with HYRNUO.

Eye problems

HYRNUO can cause problems with your eyes that could lead to temporary loss of vision.

If you have eye problems while taking HYRNUO, tell your healthcare professional immediately.

Pregnancy

- Talk to your healthcare professional before taking this medicine if you are pregnant, think you may be pregnant or are planning to have a baby.
- You should not take HYRNUO if you are pregnant. HYRNUO may harm your unborn child.
- If you are able to become pregnant:
    - Your healthcare professional will do a pregnancy test before you start taking HYRNUO.
    - Avoid becoming pregnant while taking HYRNUO because this medicine could harm the unborn child.
    - Tell your healthcare professional immediately if you become pregnant or think you are pregnant while taking HYRNUO. Your healthcare professional will decide with you whether treatment with HYRNUO should be continued or not.

Breastfeeding

- Tell your healthcare professional if you are breastfeeding or planning to breastfeed before taking this medicine.
- HYRNUO could harm your breastfed child. It is not known if HYRNUO passes into breast milk.
- You should not breastfeed during treatment with HYRNUO and for 1 week after you stop taking it.

Contraception

If you could become pregnant, you must use a highly effective method of birth control (contraception) to avoid becoming pregnant

- while you are taking HYRNUO and
- for 1 week after you stop taking it.

If you are a male with a partner who could become pregnant, you must use a highly effective method of birth control to avoid pregnancy

- while you are taking HYRNUO and
- for 1 week after you stop taking it.

If you are male and your partner becomes pregnant or might already be pregnant, while you are taking HYRNUO, tell your healthcare professional as soon as possible.

If you are a male and you have sex with a partner who is pregnant: use a condom while you are taking HYRNUO and for 1 week after you stop taking it. This is important because the semen fluid containing HYRNUO may harm the unborn child.

Talk to your healthcare professional about the right methods of birth control for you and your partner.

Liver problems

HYRNUO can cause increases in liver function blood test values which may be severe. Your healthcare professional will do blood tests to check your liver function before and during treatment with HYRNUO.

Tell your healthcare professional right away if you get any symptoms of liver problems such as:

- yellowing of the skin or white part of your eyes (jaundice)

- dark urine
- pale stools
- feel tired or weak
- nausea
- vomiting
- pain on the upper right side of your stomach

Pancreas problems

HYRNUO may cause increases in certain pancreatic lab test values (amylase and lipase). Your healthcare professional will do blood tests to check your pancreatic function before and during treatment with HYRNUO.

Tell your healthcare professional right away if you get any symptoms of pancreas problems such as:

- pain in the upper area of your stomach. This pain may spread to your back or get worse when you eat.
- weight loss
- nausea
- vomiting

Lung problems

HYRNUO may cause severe lung problems.

Tell your healthcare professional right away if you get any symptoms of lung problems during treatment with HYRNUO such as:

- cough
- fever
- shortness of breath or trouble breathing

Check-ups and testing:

HYRNUO can cause changes in blood test results. Your healthcare professional will tell you if any changes in your tests might need treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with HYRNUO:

- medicines used to treat fungal and bacterial infections such as clarithromycin, itraconazole, ketoconazole, erythromycin, rifampicin and rifabutin
- medicines used to treat HIV infections and AIDS such as cobicistat, lopinavir/ritonavir and saquinavir/ritonavir
- medicines used to treat seizures such as carbamazepine, phenytoin and midazolam
- St. John's Wort (used to treat slightly low mood and mild anxiety)

- medicines used to treat pain such as alfentanil and fentanyl
- medicines used after organ transplants such as cyclosporine, sirolimus and tacrolimus
- medicines used to treat migraines such as dihydroergotamine and ergotamine
- pimozide (used to control motor or verbal tics)
- quinidine (used to treat abnormal heart rhythms)
- digoxin (used to treat heart problems)
- methotrexate (used to treat inflammation of the joints, a skin diseased called "psoriasis," and certain kinds of cancers)
- medicines used to treat high cholesterol such as atorvastatin and rosuvastatin
- riociguat (used to treat high blood pressure in the lungs)
- granisetron (used to prevent nausea and vomiting)
- metformin (used to treat diabetes)
- cisplatin (used to treat certain kinds of cancer)
- dabigatran (used to treat blood clots)
- grapefruit and grapefruit juice

How to take HYRNUO:

- Take HYRNUO exactly as your healthcare professional tells you.
- Take the tablets with food.
- Swallow the tablets whole with a glass of water. Do not chew, break or crush tablets.
- If you vomit after taking a dose of HYRNUO, do not take an extra dose. Take your next dose at your regular time.
- Your healthcare professional may change your dose, pause or stop treatment with HYRNUO, if necessary.
- Do not change your dose or stop taking HYRNUO unless your healthcare professional tells you to. It is important to take HYRNUO for as long as your healthcare professional tells you.

Usual dose:

Take two 10 mg tablets, twice a day. This is a total of 4 tablets each day.

Do not take more than 4 tablets per day.

Overdose:

If you think you, or a person you are caring for, have taken too much HYRNUO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you missed a dose of HYRNUO, take it as soon as you remember before your next regular dose.

Do not take two doses at the same time to make up for a missed dose.

Possible side effects from using HYRNUO:

These are not all the possible side effects you may have when taking HYRNUO. If you experience any side effects not listed here, tell your healthcare professional.

- nausea with or without vomiting
- mouth sores, inflammation, or ulcer
- stomach pain
- redness, irritation, or bumps on the skin
- nail problems including:
    - in growing nails
    - nails separating from the nail bed
    - nail infection
    - nail splitting
    - color change
- itching
- dry skin
- loss of appetite
- weight loss
- low number of red blood cells (anemia) which may make you:
    - feel tired
    - look pale
    - feel your heart pumping
- feeling tired (fatigue)
- hair loss
- pain, redness, swelling or peeling of the skin of your hands and feet

Serious side effects and what to do about them:

Frequency/Side Effect/Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
Very common			
Diarrhea: having unformed stools		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Hypokalemia (low levels of potassium in the blood): diarrhea, muscle cramps, irregular heartbeat		✓	
Common			
Cardiac arrhythmia (abnormal or irregular heartbeat): an irregular heartbeat, shortness of breath, chest pain, and dizziness		✓	
Ocular toxicity: dry eyes, blurred vision, blind spots on the eye		✓	
Uncommon			
Lung problems: cough, fever, shortness of breath, trouble breathing		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store HYRNUO between 15°C to 30°C.

Keep out of reach and sight of children.

Do not use this medicine after the expiry date.

If you want more information about HYRNUO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.bayer.ca; or by calling Bayer Medical Information at 1-800-265-7382 or emailing canada.medinfo@bayer.com.

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