

Product Monograph
Including Patient Medication Information

Pr **HERNEXEOS®**

Zongertinib tablets

For Oral Use

60 mg zongertinib

Protein Kinase Inhibitor

ATC code: L01EH04

HERNEXEOS, indicated for:

- the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumours have HER2 (ERBB2) tyrosine kinase domain activating mutations and who have received 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 HERNEXEOS please refer to Health Canada's [Notice of Compliance with conditions - drug products web site](#).

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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

None at the time of most recent authorization	
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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.

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Part 1: Healthcare Professional Information

1. Indications

HERNEXEOS (zongertinib) is indicated for:

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

This indication has been issued market authorization with conditions, pending the results of a confirmatory trial to verify its clinical benefit. The authorization is based on objective response rate and duration of response (see [14.1 Clinicals Trials by Indication](#)).

1.1. Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of HERNEXEOS have not been established in pediatric patients.

1.2. Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety and efficacy were observed for elderly patients compared to patients aged below 65 years.

2. Contraindications

- HERNEXEOS 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, Composition and Packaging](#).

4. Dosage and Administration

4.1. Dosing Considerations

- Testing prior to HERNEXEOS administration
 - Patient Selection
 - Treatment with HERNEXEOS should be initiated following confirmation of a HER2 (ERBB2) mutation in a tumour specimen using a validated test (see [14.1 Clinical Trials by Indication](#)).

4.2. Recommended Dose and Dosage Adjustment

The recommended dosage of HERNEXEOS is based on body weight:

- Patients weighing less than 90 kg: 120 mg
- Patients weighing 90 kg or greater: 180 mg

- Take HERNEXEOS orally once daily.
- Treatment should be continued until disease progression or unacceptable toxicity occurs.
- Dosage adjustments due to adverse reactions
 - Recommended dose adjustments for adverse reactions are outlined in [Table 1](#). Treatment must be permanently discontinued in patients who are unable to tolerate HERNEXEOS after one dose reduction to 60 mg once daily (see [8 ADVERSE REACTIONS](#) and for further details on management of specific drug related Adverse Events (AEs) see [7 WARNINGS AND PRECAUTIONS](#)).

Table 1 Recommended dose adjustments for HERNEXEOS

Adverse reaction	CTCAE Severity	Dose adjustment
Hepatotoxicity	Grade 3 or 4 ALT and/or AST <u>without</u> increased total bilirubin	• Interrupt HERNEXEOS until recovered to ≤ Grade 1 or baseline • Resume at reduced 60 mg dose (daily)
	Grade 3 total bilirubin	• Interrupt HERNEXEOS until recovered to ≤ Grade 1 or baseline • Resume at reduced 60 mg dose (daily)
	Grade 4 total bilirubin	• Discontinue HERNEXEOS permanently
	ALT or AST ≥ 3 × ULN <u>with</u> total bilirubin ≥ 2 × ULN	• Discontinue HERNEXEOS permanently

Adverse reaction	CTCAE Severity	Dose adjustment
Diarrhea	Grade 2 continued for ≥ 2 days despite starting anti-diarrheal treatment	- Interrupt HERNEXEOS until recovered to $\leq$ Grade 1 - Resume at reduced 60 mg dose (daily)
	Grade 3 or Grade 4	- Interrupt HERNEXEOS until recovered to $\leq$ Grade 1 - Resume at reduced 60 mg dose (daily) - Permanently discontinue HERNEXEOS if despite optimal supportive care (including anti-diarrheal treatment) and treatment interruption, diarrhea does not resolve to $\leq$ Grade 1 within 14 days.
Left Ventricular Dysfunction	LVEF 40 to 50% and decrease from baseline of 10 to 19%	- Interrupt HERNEXEOS until recovered to $\leq$ Grade 1 or within 10% from baseline. - If recovered to $\leq$ Grade 1 in ≤ 4 weeks, resume HERNEXEOS at the same dose level. - If not recovered to $\leq$ Grade 1 within 4 weeks, permanently discontinue HERNEXEOS
	LVEF 20 to 39% or $\geq 20\%$ decrease from baseline	- Interrupt HERNEXEOS until recovered to $\leq$ Grade 1 or within 10% from baseline. - If recovered to $\leq$ Grade 1 in ≤ 4 weeks, resume HERNEXEOS at the reduced dose level. - If not recovered to $\leq$ Grade 1 within 4 weeks, permanently discontinue HERNEXEOS.
	Symptomatic Congestive Heart Failure	Permanently discontinue HERNEXEOS.
Interstitial Lung Disease/Pneumonitis	Grade 2	- Withhold HERNEXEOS until resolution. - Resume HERNEXEOS at reduced dose level. - Permanently discontinue HERNEXEOS for recurrent ILD/pneumonitis.
	Grade 3 or Grade 4	Permanently discontinue HERNEXEOS.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal

- Dosage adjustment for strong CYP3A inducers
 - Avoid concomitant use of strong CYP3A inducers with HERNEXEOS.
 - If concomitant use cannot be avoided, increase the HERNEXEOS dose based on body weight (see [9.4 Drug-Drug Interactions](#)):
 - Patients weighing less than 90 kg: from 120 mg to 240 mg
 - Patients weighing 90 kg or greater: from 180 mg to 360 mg

After discontinuing a CYP3A inducer, resume the HERNEXEOS dose (7 to 14 days after discontinuing the CYP3A inducer) that was taken prior to initiating the CYP3A inducer.

Special populations

- Pediatrics (< 18 years of age):
 - The safety and efficacy of HERNEXEOS have not been established in pediatric patients.
- Geriatrics (> 65 years of age)
 - No dose adjustment is required in elderly patients (see [7.1.4 Geriatrics and 10.3 Pharmacokinetics](#)).
- Hepatic impairment
 - Zongertinib is predominantly eliminated via hepatic metabolism and fecal excretion (>90%). No formal studies have been conducted to evaluate the effect of hepatic impairment on the exposure to HERNEXEOS.
 - Mild hepatic impairment (NCI-ODWG criteria: AST >ULN and total bilirubin ≤ULN; or total bilirubin >1 to ≤1.5 × ULN and any AST) has no influence on the exposure to HERNEXEOS based on a population PK analysis. No dose adjustment is required for patients with mild hepatic impairment.
 - The safety and efficacy of HERNEXEOS have not been established in patients with pre-existing moderate (total bilirubin >1.5 to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin >3 × ULN and any AST). Treatment of patients with pre-existing moderate or severe hepatic impairment with HERNEXEOS is not recommended (see [10.3 Pharmacokinetics](#)).
- Renal impairment
 - Less than 2% of a single dose of HERNEXEOS is excreted via the kidney. No clinically relevant effect on exposure was observed in patients with mild renal impairment. No dose adjustment is required in patients with mild renal impairment (eGFR ≥60 and <90 mL/min/1.73m², based on CKD-EPI formula) (see [10.3 Pharmacokinetics](#)).
 - The safety, efficacy and pharmacokinetics in patients with moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73m²), severe renal impairment (eGFR ≥15 and <30 mL/min/1.73m²) or end stage renal disease (eGFR <15 mL/min/1.73m²) have not been studied.

4.4. Administration

HERNEXEOS is for oral use. The film-coated tablets should be swallowed whole with water. HERNEXEOS can be taken with or without food (see [10.3 Pharmacokinetics](#)).

4.5. Missed Dose

If a dose of HERNEXEOS is missed, it should be taken during the same day as soon as the patient remembers. If the next dose is within 12 hours, then the missed dose must be skipped, and the next scheduled dose awaited.

5. Overdose

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and symptomatic treatment be instituted as appropriate.

In Beamion LUNG-1, an overdose in one patient who ingested 600 mg of HERNEXEOS resulted in nausea and vomiting. The patient recovered from these adverse events.

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 2 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral	Tablet/60 mg	Colloidal silicon dioxide, croscarmellose sodium, ferric oxide (yellow), glycerol mono and dicaprylocaprate, hypromellose acetate succinate, mannitol, microcrystalline cellulose, polyvinyl alcohol, sodium lauryl sulfate, sodium stearyl fumarate, talc, and titanium dioxide

Description

HERNEXEOS film-coated tablets, 60 mg are yellow, oval, biconvex tablets of a size of about 15 x 7 mm. One side is debossed with 'L6' and the other side is debossed with a Boehringer Ingelheim company symbol. They are packaged in a bottle containing 60 tablets each, along with two silica gel desiccants and a child-resistant closure.

7. Warnings and Precautions

General

Physicians should monitor patients as frequently as clinically indicated for adverse reactions and according to the instructions of [4 Dosage and Administration](#) and [9 Drug Interactions](#). For significant side effects, the treatment of symptoms and dose reduction or interruption of HERNEXEOS should be considered.

Cardiovascular

- Left Ventricular Dysfunction**

Cases of severe LVD were reported in association with HERNEXEOS treatment. Left ventricular ejection fractions (LVEF) decrease occurred with anti-HER2 therapies, including HERNEXEOS. Treatment with HERNEXEOS has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment. In the pooled safety population, LVEF decrease

occurred in 5.4% of patients treated with HERNEXEOS, including 1.8% Grade 3. 2 patients with Grade 3 LVEF decrease required permanent discontinuation. The median time to onset of decreased LVEF was 9.1 weeks (range: 2.9 to 63.1 weeks). Before initiating HERNEXEOS, evaluate LVEF and monitor at regular intervals during treatment and as clinically indicated. Interrupt, reduce the dose, or permanently discontinue HERNEXEOS based on the severity of the adverse reaction.

Driving and Operating Machinery

No studies on the effects on the ability to drive or operate machinery have been performed.

Hepatic/Biliary/Pancreatic

- **Hepatotoxicity**

In a pooled safety population (277 patients treated with 120 mg once daily of HERNEXEOS), ALT increased occurred in 16.6% of patients treated with HERNEXEOS and AST increased in 16.2%, of which 4.3% and 2.9%, respectively, were Grade 3. Grade 4 ALT increased occurred in 0.7% of patients, while no Grade 4 events of AST increased were seen. Among patients who had ALT or AST increased, first onset occurred within 12 weeks of treatment initiation in 71.7% and 68.9% of patients, respectively. Dose discontinuation for ALT and AST increased was required in 1.4% and 1.1% of patients, respectively.

In this pooled safety population, 52.3% of patients were previously treated with PD-1/PD-L1/CTLA-4 blocking antibodies. Of those, ALT increased and AST increased were reported in 17.2% and 16.6% of patients, respectively.

Liver enzymes (hepatic transaminase) and bilirubin levels should be monitored upon initiation of treatment with HERNEXEOS, once every 2 weeks during the first 8 weeks, at week 12, and periodically thereafter or as clinically indicated.

Based on the severity of the hepatic adverse reactions, the dose should be interrupted, reduced or permanently discontinued (see [4.2 Recommended Dose and Dosage Adjustment](#)).

Respiratory

- **Interstitial Lung Disease/Pneumonitis**

Cases of severe and potentially life-threatening interstitial lung disease (ILD)/pneumonitis were reported in association with HERNEXEOS treatment. In the pooled safety population, ILD/pneumonitis occurred in 1.1% of patients (N=3) treated with HERNEXEOS. The time to first onset was 41, 134 and 458 days for the three patients. One patient was able to continue therapy with HERNEXEOS. Treatment was permanently discontinued in the other two patient; out of which one patient died with unresolved pneumonitis > 30 days after discontinuing HERNEXEOS. Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Interrupt, reduce the dose or permanently discontinue HERNEXEOS based on severity of confirmed ILD/pneumonitis.

Reproductive Health

- **Fertility**

There are no data on the impact of HERNEXEOS on human fertility.

Based on findings from animal studies, HERNEXEOS may impair fertility in females of reproductive potential (see [16 Non-Clinical Toxicology](#)).

- **Contraception**

Females of reproductive potential should be advised to avoid becoming pregnant while taking HERNEXEOS and to use effective contraceptive methods during treatment with HERNEXEOS and for 10 days after the last dose.

It is unknown whether HERNEXEOS may reduce the efficacy of hormonal contraceptives. Therefore, women using hormonal contraceptives should be advised to use or add an alternative effective non-hormonal contraceptive measure.

- **Embryo-fetal toxicity**

Based on findings from animal studies and the mechanism of action, HERNEXEOS can cause embryo-fetal harm when administered to a pregnant woman. A study in pregnant rats with zongertinib has shown embryo-fetal lethality at 29-times the human exposure at the recommended dose of 120 mg daily (see [16 Non-Clinical Toxicology](#)).

Pregnancy status should be verified prior to initiation of treatment with HERNEXEOS and during treatment as appropriate. Females of reproductive potential should be advised not to become pregnant while taking HERNEXEOS (see [7.1.1 Pregnancy](#) and [7.12 Breastfeeding](#)).

7.1. Special Populations

7.1.1. Pregnancy

There is no information on the use of HERNEXEOS in pregnant women.

Based on findings from animal studies and the mechanism of action, HERNEXEOS can cause embryo-fetal harm when administered to a pregnant woman. A study in pregnant rats has shown embryo-fetal lethality at 29-times the human exposure at the recommended dose of 120 mg daily. (see [16 Non-Clinical Toxicology](#)).

Females of reproductive potential should be advised to avoid becoming pregnant while taking HERNEXEOS.

Pregnancy status should be verified in females of reproductive potential prior to treatment with HERNEXEOS and during treatment as appropriate. Female patients should be advised to notify their healthcare provider if they become pregnant or suspect they may be pregnant during therapy with HERNEXEOS. Pregnant women and females of reproductive potential should be advised of the potential risk to a foetus (see [7 Warnings and Precautions, Reproductive Health/Embryo-fetal toxicity](#)).

7.1.2. Breastfeeding

There are no data on the presence of zongertinib in human milk or its effects on either the breastfed child or on milk production.

Due to the potential for serious adverse reactions in breastfed children whose mothers are taking HERNEXEOS, women should be advised not to breastfeed during treatment with HERNEXEOS and for 10 days after the last dose.

7.1.3. Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of HERNEXEOS has not been established in pediatric patients.

7.1.4. Geriatrics

Geriatrics (>65 years of age): HERNEXEOS has been studied in patients aged 30 to 80 years. There were 32 (43%) patients 65 years of age and older in the clinical study in patients with unresectable or metastatic NSCLC of which 6 (8%) were 75 years of age or older. No overall differences in safety and efficacy were observed for elderly patients compared to patients aged below 65 years. No dose adjustment is required in elderly patients. (see [10.3 Pharmacokinetics](#)).

8. Adverse Reactions

8.1. Adverse Reaction Overview

The pooled safety population referred to in [7 Warnings and Precautions](#) reflects exposure to at least one dose of HERNEXEOS 120 mg QD in 277 patients with unresectable or metastatic solid tumors harboring HER2 mutations. Among the 277 patients who received HERNEXEOS, 55% were exposed for greater than 6 months and 12% were exposed for greater than one year. In this pooled safety population, the most common (> 20%) adverse reactions were diarrhea (51%), hepatotoxicity (25%), rash (26%), fatigue (21%), and nausea (20%). The most common ($\geq 2\%$) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (10.0%), increased alanine aminotransferase (5.3%), increased aspartate aminotransferase (4.2%), decreased potassium (2.7%), and increased gamma glutamyl transferase (2.8%).

Beamion LUNG-1:

The safety of HERNEXEOS was evaluated in Beamion LUNG-1 in 105 patients with previously treated unresectable or metastatic non-squamous NSCLC with HER2 tyrosine kinase domain (TKD) mutations; all patients had received prior platinum-based chemotherapy, and 34 patients had received prior treatment with a HER2-directed antibody drug conjugate (ADC) (see [14.1 Clinical Trials by Indication; HER2-mutant Unresectable or Metastatic NSCLC After at Least One Line of Prior Systemic Therapy](#)). Patients received HERNEXEOS as a single agent at 120 mg once daily until disease progression or unacceptable toxicity. Among patients who received HERNEXEOS, 72% were exposed for 6 months or longer and 30% were exposed for greater than one year. The median age of patients who received HERNEXEOS was 61 years (range 30 to 85), 69% were female, 40% White, 49% Asian, and 0% Black or African American; 11% had unknown race data; 1.9% were of Hispanic or Latino ethnicity; and 33% had

an Eastern Cooperative Oncology Group (ECOG) performance score of 0 and 67% had an ECOG performance score of 1.

Serious adverse reactions occurred in 34% of patients receiving HERNEXEOS. Serious adverse reactions in $\geq 2\%$ of patients included dyspnea (4.8%), pulmonary embolism (4.8%), hepatotoxicity (2.9%), and pneumonia (2.9%). Fatal adverse reactions occurred in 1% of patients who received HERNEXEOS, due to pneumonia.

Permanent discontinuation of HERNEXEOS due to an adverse reaction occurred in 2.9% of patients. Adverse reactions which resulted in permanent discontinuation of HERNEXEOS were hepatotoxicity, increased blood alkaline phosphatase, dyspnea, increased gamma-glutamyl transferase, hemoptysis, and pyrexia.

Dosage interruption of HERNEXEOS due to an adverse reaction occurred in 28% of patients. Adverse reactions which required dosage interruption in $\geq 2\%$ of patients were hepatotoxicity, decreased ejection fraction, and rash.

Dose reductions of HERNEXEOS due to adverse reactions occurred in 7% of patients. Adverse reactions which required dose reductions in $\geq 1\%$ of patients were hepatotoxicity, decreased ejection fraction, increased blood creatinine phosphokinase, increased gamma-glutamyl transferase, and decreased neutrophil count.

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 frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The safety data described below reflect exposure to HERNEXEOS 120 mg once daily in 105 patients with unresectable or metastatic NSCLC who received at least one dose in Beamion LUNG-1 (see [14.1 Clinical Trials by Indication; HER2-mutant Unresectable or Metastatic NSCLC After at Least One Line of Prior Systemic Therapy](#))

Table 3 – Adverse reactions occurring in $\geq 15\%$ of patients treated with HERNEXEOS by SOC and preferred term, sorted by frequency in Beamion LUNG-1

System organ class/preferred term	HERNEXEOS 120 mg n = 105 All Grades (%)	HERNEXEOS 120 mg n = 105 Grade $\geq 3^1$ (%)
Gastrointestinal Disorders		
Diarrhea ²	55 (52.4)	1 (1.0)
Nausea	25 (23.8)	1 (1.0)
Vomiting	16 (15.2)	2 (1.9)

System organ class/preferred term	HERNEXEOS 120 mg n = 105 All Grades (%)	HERNEXEOS 120 mg n = 105 Grade ≥3 ¹ (%)
General disorders		
Fatigue ²	26 (24.8)	0
Infections and Infestations		
Upper respiratory tract infections ²	22 (21.0)	0
Musculoskeletal and Connective Tissue Disorder		
Musculoskeletal pain ²	25 (23.8)	2 (1.9)
Respiratory, Thoracic and Mediastinal Disorders		
Cough ²	25 (23.8)	0
Dyspnea ²	16 (15.2)	6 (5.7)
Skin and Subcutaneous Tissue Disorders		
Rash ¹	34 (32.4)	1 (1.0)
Nail Disorders ¹	20 (19.0)	0

Events were graded using NCI CTCAE version 5.0.

¹ no Grade 4 or 5 adverse reactions were reported.

² Grouped term

Clinically relevant adverse reactions in <15% of patients who received HERNEXEOS included stomatitis, dry skin, pruritus, and peripheral neuropathy.

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

Clinical Trial Findings

Table 4 – Select Laboratory Abnormalities (≥ 20%) in Patients Treated with HERNEXEOS in Beamion LUNG-1.

Laboratory Parameter	HERNEXEOS N = 105	
	All Grades ¹ %	Grade 3 or 4 %
Hematology		

Laboratory Parameter	HERNEXEOS	
	N = 105	
	All Grades ¹	Grade 3 or 4
	%	%
Lymphocytes decreased	52	15
Leukocytes decreased	43	1
Hemoglobin decreased	37	0
Activated partial thromboplastin time increased	25	0
Platelets decreased	23	1
Chemistry		
Alanine aminotransferase increased	39	7
Aspartate aminotransferase increased	33	2.9
Lipase increased	30	0
Bilirubin increased	26	1
Triglycerides increased	26	0
Calcium decreased	25	0
Amylase increased	24	0
Sodium decreased	23	0
Creatinine kinase increased	22	0
Albumin decreased	21	0
Cholesterol increased	20	1.4
Alkaline phosphatase increased	20	1
Magnesium decreased	20	1
Potassium decreased	20	0

Events were graded using NCI CTCAE version 5.0.

¹ No Grade 5 adverse reactions were reported.

9. Drug Interactions

9.2. Drug Interactions Overview

Based on *in vitro* data, zongertinib is a CYP3A4, P-gp and BCRP substrate (see [10.3 Pharmacokinetics](#)). Concomitant use of zongertinib with strong CYP3A4 inducers decreases zongertinib exposure (see [9.4 Drug-Drug Interactions](#)), which may result in reduced clinical response. Co-administration of HERNEXEOS with strong CYP3A4 inducers should be avoided. If coadministration cannot be avoided, increase the HERNEXEOS dose as recommended (see [4.2 Recommended Dose and Dosage Adjustment](#)).

Based on *in vitro* data, zongertinib is a CYP3A4 inducer and time-dependent inhibitor. Zongertinib is a BCRP inhibitor. HERNEXEOS increases exposure of BCRP substrates (see [10.3 Pharmacokinetics](#)), which may increase the risk of adverse reactions related to these substrates. Co-administration of HERNEXEOS with sensitive BCRP substrates is not recommended.

9.3. Drug-Behaviour Interactions

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

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 – Established or Potential Drug-Drug Interactions

Zongertinib	Source of evidence	Effect	Clinical comment
Effect of other medicinal products on HERNEXEOS			
Strong cytochrome P450 3A4 (CYP3A4), P-gp and BCRP inhibitors and inducers, and gastric acid-reducing agents			
Strong cytochrome P450 3A4 (CYP3A4) inducers e.g., Carbamazepine, phenytoin, rifampicin, phenobarbital	CT	Co-administration of zongertinib with carbamazepine in healthy volunteers led to a decrease in zongertinib C_{max} by 43% and $AUC_{0-\infty}$ by 63%.	Co-administration of zongertinib with a strong CYP3A4 inducer decreases zongertinib exposure, which may result in reduced clinical response. Avoid concomitant use of strong CYP3A inducers with HERNEXEOS. If concomitant use cannot be avoided, increase the HERNEXEOS dose based on body weight: • Patients weighing less than 90 kg: from 120 mg to 240 mg • Patients weighing 90 kg or greater: from 180 mg to 360 mg

Strong cytochrome P450 3A4 (CYP3A4), P-gp and BCRP inhibitors e.g., Itraconazole	CT	Co-administration of zongertinib with itraconazole in healthy volunteers led to an increase in zongertinib C_{max} by 27% and AUC by 41%.	Impact of CYP3A4, P-gp and BCRP inhibition on zongertinib exposure is not expected to be clinically relevant.
Gastric acid-reducing agents e.g., Rabeprazole, omeprazole, pantoprazole	CT	The aqueous solubility of zongertinib is pH dependent with higher pH resulting in lower solubility. Co-administration of the proton pump inhibitor rabeprazole in healthy volunteers had no clinically relevant effect on zongertinib exposure.	No clinically relevant effect on zongertinib.
Effects of HERNEXEOS on other medicinal products			
Cytochrome P450 3A4 (CYP3A) substrates			
Cytochrome P450 3A4 (CYP3A4) substrates e.g., Midazolam, simvastatin, triazolam, budesonide	CT	Co-administration of zongertinib with midazolam (a sensitive CYP3A index substrate) in healthy volunteers led to an increase in midazolam C_{max} by 17% and AUC by 6%.	Zongertinib is not expected to affect the systemic exposure of drugs that are mainly metabolized by CYP3A to a clinically relevant extent

BCRP substrates e.g., Rosuvastatin, sulfasalazine	CT	Co-administration of zongertinib with rosuvastatin (a BCRP, OATP1B1/B3 substrate) in healthy volunteers led to an increase in rosuvastatin C _{max} and AUC by 3.0-fold and 2.3-fold respectively, while plasma coproporphyrin I (an endogenous OATP1B1/1B3 substrate) was not increase. Zongertinib inhibited the intestinal BCRP transporter but had no effect on OATP1B1 and OATP1B3 transporters.	Co-administration of zongertinib with sensitive BCRP substrates is not recommended and alternative medicinal products should be considered. If co-administration cannot be avoided, patients should be closely monitored for adverse reactions and recommendations provided in the BCRP substrate approved product labeling should be followed.
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Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; PBPK = Physiologically based pharmacokinetic modeling; popPK = Population pharmacokinetic modeling

9.5. Drug-Food Interactions

HERNEXEOS may be taken with or without food (see [10.3 Pharmacokinetics](#)).

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4 that may decrease zongertinib plasma concentrations and should be avoided.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Zongertinib is a selective kinase inhibitor of human epidermal growth factor 2 (HER2). In vitro, zongertinib inhibits phosphorylation of HER2, downstream signalling of HER2 (phosphorylation of ERK)

and inhibits proliferation of lung cancer cells harboring HER2 tyrosine kinase domain activating mutations. In vivo, zongertinib demonstrated anti-tumour activity in murine tumour xenograft models of NSCLC harboring HER2 tyrosine kinase domain activating mutations.

10.2. Pharmacodynamics

Cardiac electrophysiology

In Beamion LUNG-1, at 3 times the human exposure at the recommended HERNEXEOS dose of 120 mg, no mean increase in the QTc interval >20 ms was observed.

10.3. Pharmacokinetics

The pharmacokinetics of zongertinib were investigated in healthy volunteers and patients with advanced or metastatic solid tumours with HER2 aberrations.

Table 6 - Summary of zongertinib pharmacokinetic parameters in NSCLC patients

	C _{max,ss} (nmol/L)	T _{max} (h) ¹	t _{1/2} (h)	AUC _{0-24,ss} (nmol*h/L)	CL/F (mL/min)	Vd/F (L)
Multiple Dose gmean (gCV%)	3000 (37)	2 (1.5 – 6.0)	12 (21%)	34000 (35)	115 (31%)	118 (29%)

¹ Median (Min - Max)

In patients, zongertinib maximum concentration is 3000 nmol/L and the total systemic exposure is 34000 nmol*h/L following zongertinib 120 mg orally daily. Values are presented as geometric mean (CV%).

Plasma exposure after multiple oral administration of zongertinib increases approximately dose proportionally for doses between 15 mg – 150 mg twice daily and 60 mg – 360 mg once daily. Steady state was achieved within 2.5 days, and trough concentrations were maintained for at least 12 months.

With repeated once daily administration, zongertinib showed an accumulation ratio of 1.5 for AUC and 1.3 for C_{max}.

Absorption

Following oral administration of zongertinib under fasted conditions, the median time to peak plasma concentration (T_{max}) was approximately 2 hours (range: 1.5 to 6.0 hours). The geometric mean absolute bioavailability of zongertinib was 76%.

When administered with food, the absorption of zongertinib was delayed compared to fasted administration (T_{max} fasted 2 hours and T_{max} fed 4 hours). Zongertinib exposure (C_{max} and AUC) increased by approximately 26% in the presence of a high fat high calorie meal. This effect is not clinically relevant.

Distribution

The *in vitro* protein binding of zongertinib is > 99%. Zongertinib follows multiphasic disposition kinetics

in human and has an apparent (oral) volume of distribution of 118 L.

Metabolism

Based on *in vitro* metabolite profiling, CYP-mediated oxidation pathways represent 48 to 62% (mainly CYP3A4 and CYP3A5), glucuronidation 13 to 25% (mainly UGT1A4), and glutathione conjugation 13 to 26% of total hepatic metabolism. Unchanged zongertinib represented the majority (75%) of total radioactivity in plasma (AUC_{0-168h}).

Elimination

Zongertinib is a low clearance drug with apparent (oral) clearance of 115 mL/min. The renal clearance of zongertinib is <0.25 mL/min. The effective half-life calculated based on population pharmacokinetics is 12 hours.

After oral administration of a single 60 mg dose of radiolabelled zongertinib approximately 94% of the radioactive dose was recovered after dosing, with 93% recovered in feces (31% unchanged) and 1.3% recovered in urine (0.2% of the dose unchanged).

Special populations and conditions

No clinically relevant differences in the pharmacokinetics of zongertinib were observed based on age (30 – 88 years), sex, body weight (33.6 – 122 kg), race (White, Asian, Black/African American), mild renal impairment ($eGFR \geq 60$ and < 90 mL/min/ $1.73m^2$), or mild hepatic impairment (NCI-ODWG criteria: AST >ULN and total bilirubin $\leq$ ULN; or total bilirubin >1 to $\leq 1.5 \times$ ULN and any AST).

The pharmacokinetics of zongertinib have not been specifically studied in patients with moderate renal impairment ($eGFR \geq 30$ and < 60 mL/min/ $1.73m^2$), severe renal impairment ($eGFR \geq 15$ and < 30 mL/min/ $1.73m^2$), end-stage renal disease ($eGFR < 15$ mL/min/ $1.73m^2$), moderate hepatic impairment (total bilirubin > 1.5 to $3 \times$ ULN and any AST) or severe hepatic impairment (total bilirubin > $3 \times$ ULN and any AST).

11. Storage, Stability, and Disposal

Store at 15 – 25°C. Store in original container to protect from moisture. Keep the bottle tightly closed. Once opened, use within 3 months.

Part 2: Scientific Information

13. Pharmaceutical Information

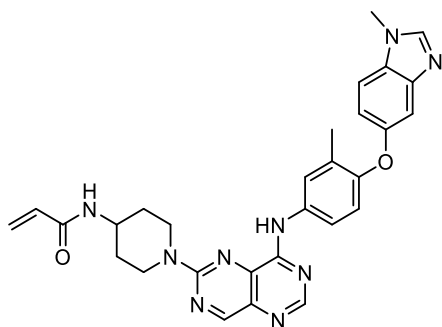
Drug Substance

Non-proprietary name of the drug substance(s): Zongertinib

Chemical name: 2-Propenamide, *N*-[1-[8-[[3-methyl-4-[(1-methyl-1*H*-benzimidazol-5-yl)oxy]phenyl]amino]pyrimido[5,4-*d*]pyrimidin-2-yl]-4-piperidinyl]-

Molecular formula and molecular mass: C₂₉H₂₉N₉O₂, 535.6 g/mol

Structural formula:



Physicochemical properties:

Melting Point: 232.4°C (onset 228.8°C)

Dissociation Constants: pK_{a1} = 3.6, pK_{a2} = 5.4

Partition Coefficient: Log P = 4.7

pH Solubility Profile: Zongertinib is slightly soluble at pH 1.2, and practically insoluble at pHs 3.6, 4.5, 5.4 and 6.8.

Pharmaceutical standard: Company Standard

Product Characteristics:

Yellow to dark yellow or orange solid, slightly hygroscopic.

14. Clinical Trials

14.1. Clinical Trials by Indication

HER2-mutant Unresectable or Metastatic NSCLC After at Least One Line of Prior Systemic Therapy

Table 7 – Summary of Patient Demographics in Clinical Trial for Patients with HER2-mutant Unresectable or Metastatic NSCLC After at Least One Line of Prior Systemic Therapy (Beamion LUNG-1)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median Age (range)	Sex
1479-0001	Single arm, open-label, multi-centre, multi-cohort	120 mg, orally, until disease progression or unacceptable toxicity	Cohort 1: 71 Cohort 5: 34	Cohort 1: 62 years (30-80) Cohort 5: 58 years (31 – 85)	Cohort 1: 70% female; 30% male Cohort 5: 65% female 35% male

HERNEXEOS was evaluated in Beamion LUNG-1, a single arm, open-label, multi-centre, multi-cohort trial at doses ranging from 30 mg to 360 mg daily (0.25 times to 3 times the recommended dose). The results for the approved recommended dose of 120 mg once daily are described below.

Cohort 1:

The efficacy of HERNEXEOS was evaluated in patients (N= 71) with unresectable or metastatic non-squamous NSCLC who had HER2 (ERBB2) mutations in the tyrosine kinase domain (TKD), received at least one line of systemic therapy that included a platinum-based chemotherapy and excluded HER2 directed targeted therapy. Patients with active brain metastases and ECOG performance status >1 were excluded.

Patients were prospectively selected for treatment with HERNEXEOS based on the presence of HER2 (ERBB2) mutations by local testing. Samples from Beamion LUNG-1 were retrospectively tested using Oncomine™ Dx Target Test (Life Technologies Corporation, Tissue-test).

The major efficacy outcome measure was objective response (OR) by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 as assessed by blinded independent central review (BICR). Additional secondary outcome measure was duration of response (DOR) based on RECIST 1.1 as assessed by BICR.

Patients were treated with HERNEXEOS until disease progression or unacceptable toxicity. The study population characteristics were: female (70%), Asian (55%), White (35%), Black or African American (0%), Hispanic or Latino (1.4%), and unknown race (10%). The baseline ECOG performance status was 0

(39%) or 1 (61%). 65% were never smokers; 100% had a mutation in the ERBB2 kinase domain. The median age was 62 years (range: 30-80). All patients had metastases at screening; 37% had stable brain metastases.

The median number of prior regimens was 1 (range: 1-10); 100% of patients received platinum-based chemotherapy, 78% immunotherapy (i.e., PD-1/PD-L1/CTLA-4 blocking antibodies). No patient had received previous treatment with HER2 targeted TKI or antibody-drug conjugate (ADC).

Efficacy results are summarized in Table 8.

Table 8 – Efficacy results for Beamion LUNG-1^a

Efficacy Parameter	HERNEXEOS (Cohort 1) N=71
Confirmed Objective Response Rate (ORR) (95% CI)	74.6% (63.4, 83.3)
Complete Response	5.6%
Partial Response	69.0%
Duration of Response (DOR)	N=53
Median, months (95% CI) ^b	14.1 (6.9, NE) ^c
% DOR ≥ 6 months ^d	56.6%

^a data cut-off: 21 October 2024

^b based on Kaplan-Meier estimate

^c NE: Non estimable

^d Based on observed duration of response

Disease control was achieved in 95.8% of patients (n=68) treated with HERNEXEOS (95% CI: 88.3, 98.6). Overall, 21.1% of patients (n=15) experienced stable disease, while 74.6% (n=53) achieved an OR.

Among the 71 patients, 26 had stable brain metastases at baseline (measurable and non-measurable). Of these, 25 patients were Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) evaluable. CNS objective response was observed in 11 of these 25 patients (44.0%, 95% CI 26.7, 62.9), including 4 patients with a CNS complete response (16.0%) and 7 patients with a CNS partial response (28.0%); 63.6% of responders had an observed DOR ≥ 6 months.

Cohort 5:

HERNEXEOS was also evaluated in 34 patients with HER2 (ERBB2) kinase domain mutation-positive non-squamous NSCLC previously treated with platinum-based chemotherapy and HER2 directed antibody-drug conjugates.

Eligibility criteria were otherwise similar to the efficacy population described above. The median age was 58 years (range: 31 - 85); 65% female, 3% Asian, 50% White, 0% Black of African American, 15% unknown race, 2.9% Hispanic or Latino. Baseline ECOG performance status was 0 (21%) or 1 (79%); 65% never smoked. 100% had a mutation in the ERBB2 kinase domain. All patients had metastatic disease and 74% had brain metastases. The median number of prior therapies was 3 (range: 1-8); 100%

received platinum-based chemotherapy, 77 % immunotherapy (anti-PD-1/PD-L1 antibody) and 2.9% of patients had received previous treatment with HER2-targeted TKI. At data cutoff of 21 October 2024, the confirmed ORR according to RECIST 1.1 based on BICR was 41.2%; 95% CI 26.4, 57.8). Of these patients, 38.2% had a partial response and 2.9% had a complete response. Median DOR was 5.3 months (95% CI 2.8, NE).

16. Non-Clinical Toxicology

General toxicology

In a 4-week dog study, redness and lesions of palate, tongue, buccal mucosa, and lips occurred at ≥ 10 mg/kg/day (≥ 0.3 times the human exposure based on AUC at the recommended dose). Histopathology demonstrated oral erosions and ulcers. At ≥ 20 mg/kg/day, reduced food intake and body-weight loss occurred. None of these findings were present following a 4-week recovery period. In a 13-week dog study, reversible redness of buccal mucosa, gums, and lower lip occurred at 6 mg/kg/day (corresponding to approximately 0.8-fold human exposure based on AUC at the recommended dose).

Genotoxicity: Zongertinib was not mutagenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay or in the combined *in vivo* Comet (liver and duodenum) assay and was not clastogenic in the *in vivo* peripheral blood Micronucleus test.

Carcinogenicity: Carcinogenicity studies have not been conducted with zongertinib.

Reproductive and developmental toxicology: In embryo-fetal developmental studies in rats and rabbits, zongertinib was administered for intervals coinciding with the first trimester period of organogenesis in humans. In the rat, zongertinib caused embryo-fetal lethality in a non-pivotal dose-range finding study approximately 29 times the human exposure based on AUC at the recommended dose. In the pivotal study, a non-adverse developmental delay was observed as reduced fetal weight in combination with reduced ossification and retardation of the urinary system at doses up to 19 times the human exposure based on AUC at the recommended dose. In the rabbit, zongertinib caused dose dependent maternal toxicity at all tested dose levels but no embryo-fetal toxicity was observed (at 2.4 times the human exposure based on AUC at the recommended dose).

Dedicated animal fertility studies have not been conducted with zongertinib. In a repeat-dose toxicity study partially reversible effects on female reproductive organs (uterus atrophy, hyperplasia/hyperkeratosis of cervix and vagina) were observed in rats (approximately 17 times the human exposure based on AUC at the recommended dose). In male rats reversible effects (atrophy of the prostate gland) and non-reversible effects (vacuolation in the testis) were observed at doses ≥ 8.4 times and ≥ 5.7 times, respectively, based on the human exposure at the recommended dose following a 4-week recovery period.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **HERNEXEOS®**

Zongertinib tablets

This Patient Medication Information is written for the person who will be taking **HERNEXEOS**. 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 **HERNEXEOS**, talk to a healthcare professional.

What **HERNEXEOS** is used for:

For the following indication **HERNEXEOS** 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.

HERNEXEOS is used to treat adult patients with a type of lung cancer called "non-small cell lung cancer (NSCLC)" when:

- the cancer is caused by a change in a gene called human epidermal growth factor receptor 2 (HER2, also referred to as *ERBB2*).
- you have tried another treatment for your cancer
- the cancer cannot be removed by surgery
- the cancer has spread to other parts of the body (metastatic)

Your healthcare professional will do a test to make sure that **HERNEXEOS** 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 **HERNEXEOS** works:

HER2 (ERBB2)-mutant non-small cell lung cancer (NSCLC) is a type of lung cancer caused by a change in the HER2 (ERBB2) gene. This change can make cancer cells grow and divide quickly.

HERNEXEOS is a treatment that targets the HER2 protein. It works by attaching to and blocking this

protein's signal. This helps slow down or stop the growth of cancer cells driven by the HER2 (ERBB2) mutation.

The ingredients in HERNEXEOS are:

Medicinal ingredient: zongertinib

Non-medicinal ingredients: Colloidal silicon dioxide, croscarmellose sodium, ferric oxide (yellow), glycerol mono and dicaprylocaprate, hypromellose acetate succinate, mannitol, microcrystalline cellulose, polyvinyl alcohol, sodium stearyl fumarate, sodium lauryl sulfate, talc, and titanium dioxide

HERNEXEOS comes in the following dosage form:

Tablets: 60 mg

Do not use HERNEXEOS if:

- You are allergic to zongertinib, or any other ingredients in HERNEXEOS or its container.

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

- have or have had liver problems.
- have or have had heart problems.

Other warnings you should know about:

- **Liver Problems:**
 - Your healthcare provider will do blood tests to check your liver function during your treatment with HERNEXEOS. Tell your healthcare provider right away if you have any symptoms of a liver problem, which may include:
 - yellowing of your skin or the white part of your eyes (jaundice);
 - dark or brown (tea coloured) urine;
 - pain on the upper right side of your stomach area (abdomen);
 - bleeding or bruising more easily than normal;
 - feeling very tired.
- **Diarrhea**
 - HERNEXEOS may cause diarrhea (loose stools) during treatment. This may start within 1-2 weeks of treatment and can be severe or persistent.
 - If you get diarrhea during treatment, tell your healthcare professional. They may need to give you medicines to treat the diarrhea.
- **Female Patients:**

Pregnancy and birth control

 - If you are able to get pregnant or think you are pregnant, there are specific risks **you must** discuss with your healthcare professional.
 - Your healthcare professional will do a pregnancy test before you start treatment with HERNEXEOS.
 - Avoid becoming pregnant while taking HERNEXEOS.

- You should use an effective form of non-hormonal birth control during treatment with HERNEXEOS and for 10 days after your last dose.
 - Birth control methods that contain hormones (such as birth control pills, injections or transdermal system patches) may not work well during treatment with HERNEXEOS.
 - Talk to your healthcare professional about birth control methods that might be right for you during this time.
- Tell your healthcare provider right away if you become pregnant or think you are pregnant while taking HERNEXEOS.

Breastfeeding

- Do NOT breastfeed during treatment and for 10 days after your last dose of HERNEXEOS. It is not known if HERNEXEOS passes into your breast milk.
- Talk to your healthcare professional about the best way to feed your baby during treatment with HERNEXEOS.

- **Fertility in Females:**

- HERNEXEOS may cause fertility problems in females, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.

- **Check-ups and testing:**

- You will have regular visits with your healthcare professional before and during treatment with HERNEXEOS. They will:
 - Do blood tests to check your liver function. This will be done at the beginning of treatment, once every 2 weeks during the first 8 weeks of treatment, at week 12 and periodically as needed.
 - Do tests to monitor your heart before starting treatment and regularly during treatment as needed.
 - check for signs of side effects, including lung problems

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 HERNEXEOS:

- carbamazepine, phenobarbital or phenytoin, medicines used to treat seizures;
- prasugrel, medicine used to prevent heart attack or stroke;
- rifampicin, an antibiotic used to treat tuberculosis;
- rosuvastatin, medicine used to treat high cholesterol and prevent heart disease;
- sulfasalazine, medicine used to treat arthritis and ulcerative colitis;
- St. John's Wort, a herbal medicine used to treat depression

How to take HERNEXEOS:

- Take HERNEXEOS exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take HERNEXEOS one time a day, at the same time each day for as long as your healthcare professional has prescribed.
- Take HERNEXEOS with or without food.
- Swallow tablets whole with water.

Usual dose:

Your healthcare professional will decide on the best dose for you.

The usual dose is based on body weight:

- Patients weighing **less than** 90 kg: 120 mg (two 60 mg tablets)
- Patients weighing **more than** 90 kg: 180 mg (three 60 mg tablets)

Your dose will also depend on your current health, if you take certain other medications, or if you have certain side effects. Your healthcare professional will monitor your health throughout your treatment and may interrupt, reduce or stop your dose.

Overdose:

If you think you, or a person you are caring for, have taken too much HERNEXEOS, 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 miss a dose of HERNEXEOS by:

- **less than** 12 hours of your usual time, take it as soon as you remember.
- **more than** 12 hours of your usual time, skip the missed dose and take your next dose at your next scheduled time.

Possible side effects from using HERNEXEOS:

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

Side effects may include:

- diarrhea
- rash
- increased liver function tests
- nausea, vomiting
- nail problems
- feeling tired
- muscle pain
- upper respiratory tract infection, such as a cold
- shortness of breath
- cough

HERNEXEOS may cause abnormal blood test results. Your healthcare professional will tell you if your blood tests are abnormal and if you need treatment to correct these side effects.

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 (loose stools)	✓		
Rash (skin redness, bumps, itching)	✓		
Nausea (feeling sick)	✓		
Nail problems (brittle or painful nails, nail changes)	✓		
Changes in liver tests (seen on bloodwork, may not cause symptoms)		✓	
Dry skin	✓		
Itching (pruritic)	✓		
Liver problems, including liver injury: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, unusual tiredness, or itching all over the body.		✓	
Common			
Mouth sores: pain, ulcers, difficulty swallowing)	✓		
Uncommon			
Heart problems: feeling like your heart is pounding or racing, dizziness, tiredness, feeling lightheaded, shortness of breath, loss of consciousness, coughing, or swelling of your legs, ankles, or feet		✓	
Lung problems: new or worsening trouble breathing, shortness of breath, cough, or fever		✓	

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 at 15 to 25°C. Store in the original container to protect from moisture. Keep the bottle tightly closed. Once opened, use within 3 months.
- Keep out of reach and sight of children.
- Do not use this medicine after the expiry date which is stated on the carton.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

If you want more information about HERNEXEOS:

- 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 (<https://www.boehringer-ingelheim.ca>); or by calling 1-800-263-5103, extension 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd. The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

Date of Authorization: 2026-09-24