EFFECTIVELY MANAGING
LORVIQUA ADVERSE REACTIONS

This guide provides an overview of the safety profile of Lorviqua and suggests management strategies for select adverse recreations.

Recommendations are based on more then 5 years of 1L clinical trial data and real world experience.[1]

INDICATION

LORVIQUA® IS INDICATED FOR THE TREATMENT OF ADULT PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) WHOSE TUMORS ARE ANAPLASTIC LYMPHOMA KINASE (ALK)-POSITIVE[2]

For further information on warnings, precautions and full list of Adverse effects please refer to the latest approved prescribing information

PP-LOR-ISR-0109

1L=first line.

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DESIGNED FOR PROLONGED TREATMENT BENEFIT[1,2]

With LORVIQUA, there was a 72% reduction in risk of progression or death vs crizotinib at Year 1 (HR, 0.28; 95% CI 0.19-0.41); *P*<0001). At Year 3, the reduction in risk of progression or death was 73% vs crizotinib (HR, 0.27; 95% CI 0.18-0.39).[2-4]

LORVIQUA offers >5 years PFS in 1L *ALK*+ advanced non-small cell lung cancer (aNSCLC), the longest PFS ever reported in advanced lung cancer[1]

LORVIQUA is active against a broad spectrum of *ALK* mutations and delays their occurrence.[5,6]

LORVIQUA demonstrated superior PFS vs crizotinib[1]

Median PFS with LORVIQUA was not reached at 5 years vs 9.1 months with crizotinib (HR, 0.19; 95% CI, 0.13 to 0.27).

At the 5-year follow-up analysis of the Phase 3 CROWN trial[1]

60% of patients were alive and progression free vs 8% with crizotinib

92% of patients remained free of CNS progression vs 21% with crizotinib

LORVIQUA has a distinct and manageable safety profile backed by 5 years of safety data[1]

- **Only 5% patients discontinued LORVIQUA due to treatment-related adverse reactions,** which occurred during the first 26 months[1]
- ARs with Lorviqua are largely manageable with concomitant therapies, temporary treatment interruptions, and/or dose reductions[1,4]
- The safety profile of LORVIQUA was consistent with that of the primary analysis. No new safety signals emerged after 5 years[1]
- At 5-year follow-up, **dose reductions did not compromise systemic or intracranial efficacy[1]**
- Most patients were able to stay on treatment with LORVIQUA for more than 5 years in the clinical trial with ARs actively managed[1,4]

LORVIQUA ARs CAN BE MANAGED WITH A SIMPLE 4-STEP APPROACH[4]

Prepare	Monitor	Manage	Reassess
patients and caregivers about what to expect while taking LORVIQUA	for ARs commonly associated with LORVIQUA at baseline and with each follow-up visit	with mitigation strategies first, then dose holds, and potentially dose reductions	at least monthly, all potential ARs, any experienced ARs, and any required dose modifications

Regardless of how bothersome the AR is to the patient, there are straightforward management strategies, including lifestyle modifications and dose adjustments, that can help patients maintain treatment benefits while addressing ARs.[4]

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TYPICAL TIMELINE OF LORVIQUA ADVERSE REACTIONS[4]

Median time to onset and duration of select ARs*

*The values listed here represent median time to first occurrence for each AR. There is a distribution in which some may occur earlier or later than these median values.[4]

The earlier symptoms are detected, the sooner interventions such as dose adjustments can be made to help patients experience relief without compromising efficacy.[4]

ALK=anaplastic lymphoma kinase; aNSCLC= advanced non-small cell lung cancer; AR=adverse reaction; CI=confidence interval; CNS=central nervous system; HR=hazard ratio; PFS=progression-free survival.

OVERVIEW

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DOSING GUIDE

Starting dose[2]

- The recommended dose is 100 mg orally, once daily
- Patients should take a missed dose as soon as it is remembered unless it is less than four hours before their next dose is due, in which case the missed dose should not be taken
- Patients should not take two doses at the same time to make up for missed doses

Dose modification[2,4]

- When dose reduction is appropriate, the initial starting dose of LORVIQUA of 100 mg daily can be reduced to 75 mg daily dose, with a subsequent drop by 25 mg
- A low threshold should be used to initiate dose reductions, especially given the preserved clinical efficacy of reduced doses of LORVIQUA[4]
- If the patient is unable to tolerate the 50 mg dose, LORVIQUA should be permanently discontinued

Not actual size of tablets

CONTRAINDICATIONS, PRECAUTIONS AND SPECIAL POPULATIONS

Contraindications[2,4]

- Hypersensitivity to LORVIQUA or to any of the excipients listed in section 11 of the Israeli PI
- Concomitant use of strong CYP3A inducers (see drug interactions on page 6)

Special warnings and precautions for use[2]

The following have been reported in patients receiving LORVIQUA:

Hyperlipidaemia

- Monitor serum cholesterol and triglycerides before initiating LORVIQUA, 1 and 2 months after initiating LORVIQUA, and periodically thereafter

Hypertension

- Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with LORVIQUA

CNS effects

- Dose modification or discontinuation may be required for patients who develop CNS effects

Cardiac

- Monitor ECG prior to initiating LORVIQUA and periodically thereafter

Interstitial lung disease (ILD)/ pneumonitis

- Any patient presenting with worsening of respiratory symptoms indicative of ILD pneumonitis should be promptly evaluated for ILD/pneumonitis

Lactose intolerance

- This medicinal product contains lactose as an excipient
- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose galactose malabsorption should not take this medicinal product

Hyperglycemia

- Assess fasting serum glucose prior to initiation of LORVIQUA and monitor periodically thereafter

Pregnancy and contraception

- Advise females of reproductive potential to use an effective non-hormonal method of contraception, since LORVIQUA can render hormonal contraceptives ineffective, during treatment with LORVIQUA and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with LORVIQUA and for 3 months after the final dose

Fertility

- Male fertility may be compromised during treatment with LORVIQUA.

Breastfeeding

- It is unknown whether LORVIQUA and its metabolites are excreted in human milk. A risk to the newborns/ infants cannot be excluded.
- LORVIQUA should not be used during breast feeding. Breast feeding should be discontinued during treatment with LORVIQUA and for 7 days after the final dose

Dietary sodium

- LORVIQUA contains less than 1 mmol sodium (23 mg) per 25 mg or 100 mg tablet. Patients on low sodium diets should be informed that this product is essentially “sodium free”.

Special populations[2]

Hepatic impairment

- No dose adjustments are required in mild hepatic impairment
- The recommended dose of LORVIQUA has not been established for patients with moderate or severe hepatic impairment

Elderly population

- Although data are limited, no clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients

Renal impairment

- No dose reduction is needed for patients with mild or moderate renal impairment (CLcr 30 to 89 mL/min)
- Reduce the recommended dose of LORVIQUA for patients with severe renal impairment (CLcr 15 to < 30 mL/min) from 100 mg to 75 mg orally once daily.

Paediatric population

- The safety and effectiveness of LORVIQUA in pediatric patients have not been established

CONTRAINDICATIONS, PRECAUTIONS AND SPECIAL POPULATIONS

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IMPORTANT DRUG INTERACTIONS[2]

CYP3A inducers

- LORVIQUA® plasma concentrations is decreased by concomitant use with strong CYP3A inducers
- Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have also been observed with the concomitant use of LORVIQUA and strong CYP3A inducers
- LORVIQUA is contraindicated in patients taking strong CYP3A inducers. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating LORVIQUA
- Avoid concomitant use of moderate CYP3A inducers with LORVIQUA. If concomitant use with moderate CYP3A inducers is unavoidable, increase the LORVIQUA dose to 125 mg once daily.

CYP3A inhibitors

- Concomitant use of strong CYP3A inhibitors increased LORVIQUA plasma concentrations
- Avoid the concomitant use of LORVIQUA with a strong CYP3A inhibitor
- If a strong CYP3A inhibitor must be co-administered, the starting dose of LORVIQUA should be reduced from 100 mg once daily to 75 mg once daily.

CYP3A substrates

- Concomitant use of LORVIQUA decreases the concentration of CYP3A substrates which may reduce the efficacy of these substrates
- LORVIQUA is considered a moderate CYP3A inducer. Avoid concomitant use of LORVIQUA with CYP3A substrates, where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with approved product labeling.

P-glycoprotein (P-gp) Substrates

- Concomitant use of LORVIQUA decreases the concentration of P-gp substrates which may reduce the efficacy of these substrates. LORVIQUA is considered a moderate P-gp inducer. Avoid concomitant use of LORVIQUA with P-gp substrates for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the P-gp substrate dosage in accordance with approved product labeling.

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GENERALLY MANAGEABLE SAFETY PROFILE WITH LARGELY MILD-TO-MODERATE ADVERSE REACTIONS

Adverse reactions (any grade) occurring in ≥20% of patients treated with LORVIQUA (N=149)[1]

Adverse drug reactions	All Grades	Grades 3-4
Hypercholesterolaemia[a]	72%	21%
Hypertriglyceridaemia[b]	66%	25%
Edema[c]	57%	4%
Peripheral neuropathy[d]	44%	1%
Weight increased	44%	23%
Fatigue[e]	30%	1%
Arthralgia	28%	1%
Cognitive effects[f]	28%	3%
Diarrhoea	23%	2%
Mood effects[g]	21%	1%
Hypertension	26%	12%
Dyspnea	23%	3%
Headache	22%	0%
Cough	20%	0%
Pyrexia	20%	1%

[a]Hypercholesterolaemia (including blood cholesterol increased, hypercholesterolaemia).

[b]Hypertriglyceridaemia (including blood triglycerides increased, hypertriglyceridaemia).

[c]Edema (including generalised oedema, edema, edema peripheral, peripheral swelling, swelling).

[d]Peripheral neuropathy (including burning sensation, dysaesthesia, formication, gait disturbance, hypoaesthesia, motor dysfunction, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, sensory disturbance).

[e]Cognitive effects (including events from SOC Nervous system disorders: amnesia, cognitive disorder, dementia, disturbance in attention, memory impairment, mental impairment; and also including events from SOC Psychiatric disorders: attention deficit/hyperactivity disorder, confusional state, delirium, disorientation, reading disorder). Within these effects, terms from SOC Nervous system disorders were more frequently reported than terms from SOC Psychiatric disorder.

[f]Fatigue (including asthenia, fatigue).

[g]Mood effects (including affective disorder, affect lability, aggression, agitation, anger, anxiety, bipolar I disorder, depressed mood, depression, depressive symptom, euphoric mood, irritability, mania, mood altered, mood swings, panic attack, personality change, stress).

Based on data from 60-month follow up of 149 patients who received LORVIQUA 100 mg once daily in the phase 3 CROWN trail. Date cutoff: 31 October 2023.[1]

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PROMPTLY AND EFFICIENTLY MANAGE CNS ADVERSE REACTIONS

LORVIQUA is specifically designed to cross the blood-brain barrier and has shown intracranial efficacy with deep, durable responses[1,7,8]:

- CNS ARs are observed as primarily cognitive, mood, speech, and psychotic effects[4]
- CNS ARs were experienced by 42% of patients[1]
- **The majority of CNS ARs were mild (grade 1/2)** and improved or resolved with either no intervention, concomitant medication, dose modification or a combination.[4]
- 2% of permanent treatment discontinuations were due to CNS ARs[1,4]

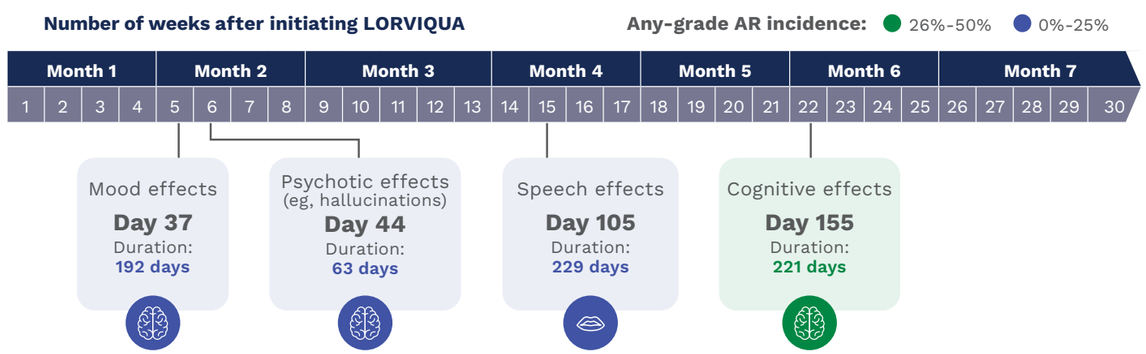
Encourage patients and caregivers to watch out for any neurocognitive symptoms, including[4]:

- Difficulty remembering (eg, sluggish thoughts, fogginess, trouble connecting the dots)
- Depression
- Anxiety
- Irritability
- Difficulty speaking or slow speech
- Hallucinations
- Impaired judgement
- Changes in mood or interactions with family members

Active monitoring and early detection of CNS adverse reactions is critical to defining if any intervention is necessary, and the type needed.[4]

Dose modifications are a demonstrated effective way to manage reactions without compromising efficacy.[4]

Incidence, median time to onset, and duration of CNS ARs[4]



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RECOMMENDED MANAGEMENT OF CNS ARs

Most CNS ARs did not require any intervention[5]

Toxicity	How bothersome is the toxicity?[a]			Reassess regularly until stable/improved
	Not bothersome	Mild to moderately bothersome	Severely bothersome	
CNS (cognitive, mood, speech, psychotic)	Toxicity management	Pause → 25 mg	Pause → 25 mg	If worse, 25 mg If stable or better, Continue

Pause: LORVIQUA dose interruption
Continue: maintain same LORVIQUA dose
25 mg Reduce: LORVIQUA dose reduction (by 25-mg decrements)

[a]As severity increases, add management from left to right. Note that all ARs are subjective; if a patient experiences a moderately bothersome AR that is functionally debilitating or functionally detrimental, this may be interpreted as being severely bothersome after discussion with the patient and healthcare provider. CNS toxicities tend to be bothersome and less likely to respond to mitigation strategies; therefore, early dose reduction in combination with temporary dose interruption may be preferred, and dose escalation after the resolution of symptoms is not recommended.[4]

MITIGATION STRATEGIES FOR CNS ARs

The majority of CNS ARs did not require pharmacologic interventions[4,9]

Non-pharmacologic	Reassess and manage other causes of neurocognitive impairment **Strategies to minimise impact include:** • Setting reminders • Meditation • Mindfulness • Cognitive behavioral therapy
Pharmacologic	• Early dose interruption and dose reduction **For rare instances of severe, refractory CNS effects:** Consider a psychiatrist for pharmacologic management (eg, antipsychotics, antidepressants)

Advise patients and caregivers to notify their healthcare team immediately if they experience or observe any new or worsening CNS adverse reactions. Early identification may help alleviate symptoms.[4]

CNS ARs

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HYPERLIPIDAEMIA CAN BE MANAGED BY PRESCRIBING THE APPROPRIATE STATIN

Routinely monitoring patients' lipid levels is critical for effective management[4]

Hyperlipidaemia is classified as hypercholesterolaemia and hypertriglyceridaemia:

- **Hypercholesterolaemia** (ie, elevation in total cholesterol)
- **Hypertriglyceridaemia** (ie, elevation of blood triglyceride levels)
- 72% of patients experienced hypercholesterolaemia and 66% of patients experienced hypertriglyceridaemia[1]
- Incidences of hyperlipidaemia were mostly grades 1 (mild) and 2 (moderate) and could generally be managed with standard lipid-lowering agents without withholding or interrupting LORVIQUA[3,4]
- Hyperlipidemia led to permanent discontinuation in 1% of patients[4]
- Despite a higher rate of hyperlipidaemia, cardiovascular AEs (28%) were similar between the treatment groups[1]

Incidence, median time to onset, and duration of hyperlipidaemia[4]

Number of weeks after initiating LORVIQUA

Any-grade AR incidence: 76%-100%

Month 1				Month 2				Month 3					Month 4				Month 5				Month 6				Month 7				
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30

Hyperlipidaemia
Day 15
Duration:
427-451 days

Since hyperlipidaemia causes no visible or observable symptoms, patients and caregivers should understand the importance of keeping up with blood tests, as recommended by their physician.[4]

RECOMMENDED MANAGEMENT OF HYPERLIPIDAEMIA ARs

Hyperlipidaemia of all grades can be effectively managed by introducing a lipid-lowering therapy or adjusting the current lipid-lowering therapy[4]

Prepare	Monitor (at 1 month)		Reassess regularly until stable/improved
Measure lipid levels **If elevated, start/increase** lipid-lowering agent	Normal lipid levels	**Monitor lipid levels at each follow-up visit**	**If hyperlipidaemia is uncontrolled, increase, change, or add lipid-lowering therapy** If maximal doses of lipid-lowering agents are reached, lower LORVIQUA dose by 25 mg ▼ 25 mg
	Elevated lipid levels **Total cholesterol ULN-500 mg/dL (12.93 mmol/L) or triglycerides 150-1000 mg/dL (1.71-11.29 mmol/L)**	**Begin, increase, or change lipid-lowering therapy**	
	Life-threatening elevated lipid levels **Total cholesterol >500 mg/dL (12.93 mmol/L) or triglycerides >1000 mg/dL (11.29 mmol/L)[a]**	Initiate lipid-lowering therapy and pause LORVIQUA until **total cholesterol is <400 mg/dL (10.34 mmol/L) and triglycerides are <500 mg/dL (5.65 mmol/dL)[a]** and then restart	

Pause: LORVIQUA dose interruption

Continue: maintain same LORVIQUA dose

▼ 25 mg Reduce: LORVIQUA dose reduction (by 25-mg decrements)

CYP=cytochrome P450; PO=by mouth; QD=once-daily.

[a]Cholesterol and triglyceride threshold values can be modified based on overall cardiovascular risk and life expectancy.[4]

[b]Pravastatin, or rosuvastatin are suggested for use with lorlatinib based on their low involvement with specific cytochrome P450 enzymes that interact with lorlatinib (eg, CYP3A4). Fenofibrate has the least involvement with CYP enzymes, followed by fish oils and nicotinic acid.[4]

MITIGATION STRATEGIES FOR HYPERLIPIDAEMIA ARs

Pharmacologic intervention with a statin is recommended to help manage hyperlipidemia[4]

Non-pharmacological	Dietary changes may be employed; however, hyperlipidaemia typically requires pharmacologic strategies
Pharmacological	**Choose one of the following statins[b]:** Pravastatin (400 mg PO QD) Rosuvastatin (5-10 mg PO QD for moderate intensity) (20-40 mg PO QD for high intensity) **Despite maximum statin dose:** If hyperlipidaemia is inadequately controlled ⇨ Add ezetimibe If triglycerides remain >500 mg/dL (5.65 mmol/L) ⇨ Add fibrates/fish oil

HYPERLIPIDAEMIA

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EFFECTIVELY MANAGING EDEMA AND WEIGHT GAIN

Determining how bothered patients are by edema can be helpful in determining the appropriate mitigation approach[4]

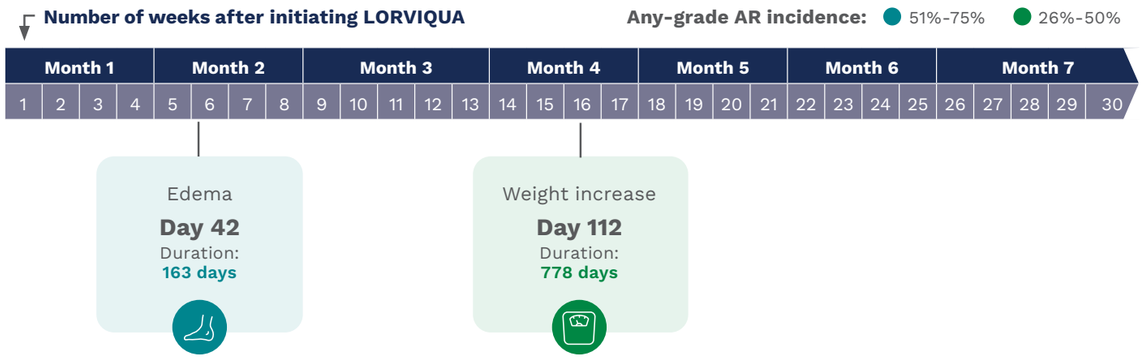
- Edema is not unique to LORVIQUA; it has been reported with other ALK TKIs[1,4]
- Most patients experienced either mild (grade 1) or moderate (grade 2) edema, and 4% of patients had a severe (grade 3/4) event[4]
- Edema was the most common reason for dose reduction (7%)[4]

Patients may be the first to notice weight gain and can take an active role in managing it[4]

- Weight gain is not isolated to treatment with LORVIQUA; it has also been observed in other TKIs
- Weight gain rarely led to dose modifications (1% of patients), and no discontinuations due to weight gain were reported
- Prior to gaining weight, some patients may have incurred unintentional weight loss due to the underlying disease, so it may be preferable to determine a baseline that is the patient's "healthy weight" prior to cancer diagnosis

Food intake counseling, dietary advice, and/or addition of exercise may be helpful in managing weight gain.[4]

Incidence and median time to onset and median duration of edema and weight increase[4]



TKI=tyrosine kinase inhibitor.

RECOMMENDED MANAGEMENT OF EDEMA AND WEIGHT GAIN

Lifestyle modifications are recommended to help manage edema and weight gain[4]

Toxicity	How bothersome is the toxicity?[a]			Reassess regularly until stable/improved
	Not bothersome	Mild to moderately bothersome	Severely bothersome	
Edema	Lifestyle modifications and therapeutic intervention		⏸ → ▼25 mg	If worse, ▼25 mg
Weight gain	Lifestyle modification and toxicity management			If stable or better, ▶

⏸ Pause: LORVIQUA dose interruption

▶ Continue: maintain same LORVIQUA dose

▼25 mg Reduce: LORVIQUA dose reduction (by 25-mg decrements)

[a]As severity increases, add management from left to right. For edema that is severely bothersome, consider lifestyle modifications, therapeutic intervention, dose interruption, and dose reduction. If weight gain and edema are experienced together, edema should be managed first, as a reduction in edema can influence body weight. Dose modifications for weight gain alone are only recommended if weight continues to be severely bothersome after the addition of lifestyle modifications[4]

MITIGATION STRATEGIES FOR EDEMA AND WEIGHT GAIN

Non-pharmacologic interventions are recommended to help manage edema and weight gain[4]

	Edema	Weight gain
Non-pharmacologic mitigation strategies	Rule out alternative causes, such as cardiac (heart failure), renal, and thyroid causes. Examples of helpful interventions include compression garments, raising the affected area above the heart, increased exercise, limiting dietary salt, physiotherapy, and lymphoedema massage.	Food intake counseling, dietary advice, and/or the addition of exercise can be helpful.
Pharmacologic mitigation strategies	There is limited scientific evidence to support the use of diuretics. However, based on clinical experience managing edema, diuretics can be used as an option for management. If persistent, healthcare providers are encouraged to consult with the respective specialists (ie, cardiologist, endocrinologist, etc), and other causes should be considered in order to help identify additional solutions.	Currently, there are no data on the use of semaglutide or other incretins in the management of lorlatinib-induced weight gain. Any use of semaglutide or other incretins should be per approved indications and under expert physician management of the potential side effects.

EDEMA AND WEIGHT GAIN

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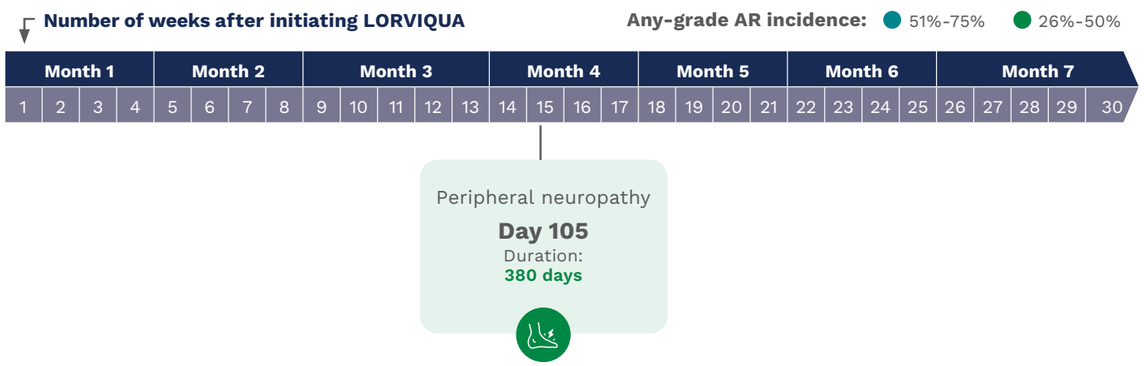
WITH THE RIGHT MANAGEMENT, PERIPHERAL NEUROPATHY SYMPTOMS ARE TYPICALLY MILD AND REVERSIBLE[4]

Monitor patients for symptoms of peripheral neuropathy such as tingling, numbness, and pain at night in the fingers and toes[4]

- LORVIQUA-associated peripheral neuropathy is typically mild and reversible
- Dose reductions and discontinuations due to peripheral neuropathy were uncommon, reported in 3% and 1% of patients, respectively
- Prior to initiating therapy, patients should be assessed for any underlying causes of peripheral neuropathy (such as diabetes) and reevaluated for signs and symptoms at each follow-up visit

Peripheral neuropathy can be managed with lifestyle interventions or with the addition of vitamins B1 and B6.[4]

Incidence and median time to onset and median duration of peripheral neuropathy[4]



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RECOMMENDED MANAGEMENT OF PERIPHERAL NEUROPATHY

Effective management of peripheral neuropathy[4]

Toxicity	How bothersome is the toxicity?[a]			Reassess regularly until stable/improved
	Not bothersome	Mild to moderately bothersome	Severely bothersome	
Peripheral neuropathy	Toxicity management	Pause → Continue OR ▼25 mg	Pause → ▼25 mg	If worse, ▼25 mg If stable or better, Continue

Pause: LORVIQUA dose interruption
Continue: maintain same LORVIQUA dose
▼25 mg Reduce: LORVIQUA dose reduction (by 25-mg decrements)

[a]As severity increases, add management from left to right. For peripheral neuropathy that is not bothersome consider lifestyle and/or pharmacological interventions. For mild to moderately bothersome neuropathy dose interruption should be considered until symptoms resolve and treatment reintroduced at the same or reduced dose while for patients with severely bothersome or recurrent peripheral neuropathy, treatment should be temporarily interrupted while maximizing mitigation strategies until symptoms improve, and treatment rechallenged at a lower dose.[4]

MITIGATION STRATEGIES FOR PERIPHERAL NEUROPATHY

Consider how bothersome peripheral neuropathy is to the patient in choosing a non-pharmacologic or pharmacologic mitigation strategy[4]

Non-pharmacologic mitigation strategies	A night splint may improve carpal tunnel syndrome. Peripheral neuropathy associated with edema (particularly in the upper extremities) may respond to compression garments, raising the affected area above the heart, increased exercise, limiting dietary salt, physiotherapy, and lymphoedema drainage/massage.
Pharmacologic mitigation strategies	Treatments: vitamin B1 and vitamin B6 and medications (gabapentin or pregabalin) may provide symptom relief.

References: 1. Solomon BJ, Liu G, Felip E, et al. Lorlatinib versus crizotinib in patients with advanced ALK-positive non-small cell lung cancer: 5-year outcomes from the phase III CROWN study. J Clin Oncol. 2024 in press. doi:10.1200/JCO.24.00581. **2.** LORVIQUA® Israeli latest approved Prescribing Information. **3.** Shaw AT, Bauer TM, de Marinis F, et al; CROWN Trial Investigators. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N Engl J Med.* 2020;383(21):2018-2029. **4.** Liu G, Mazieres J, Stratmann J, et al. A pragmatic guide for management of adverse events associated with lorlatinib. *Lung Cancer.* 2024;191:107535. **5.** Shaw AT, Solomon BJ, Besse B, et al. ALK resistance mutations and efficacy of lorlatinib in advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer. *J Clin Oncol.* 2019;37(16):1370-1379. **6.** Gainor JF, Dardaei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov.* 2016;6(10):1118-1133. **7.** Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK positive non-small cell lung cancer: results from a global phase 2 study. *Lancet Oncol.* 2018;19(12):1654-1667. **8.** Bauer TM, Shaw AT, Johnson ML, et al. Brain penetration of lorlatinib: cumulative incidences of CNS and non-CNS progression with lorlatinib in patients with previously treated ALK-positive non-small-cell lung cancer. *Target Oncol.* 2020;15(1):55-65. **9.** Solomon BJ, Bauer TM, Ignatius Ou SH, et al. Post hoc analysis of lorlatinib intracranial efficacy and safety in patients with *ALK*-positive advanced non-small-cell lung cancer from the phase III CROWN study. *J Clin Oncol.* 2022;40(31):3593-3602.

PERIPHERAL NEUROPATHY

A USEFUL CHECKLIST FOR MANAGING SELECT ADVERSE REACTIONS

	What To Look For	Management Strategies to Consider
PRIOR TO INITIATING LORVIQUA*	☐ Central Nervous System (CNS) assessment (*ie, baseline cognitive functioning, mood, and speech*) ☐ Cardiovascular function assessment ☐ Blood pressure assessment ☐ Fasting serum glucose assessment ☐ Serum cholesterol and triglyceride assessment	• Open communication between patients and caregivers while preparing for treatment • AR management education, ensuring patient and caregiver know to report AR
MONTH <1	**Hyperlipidemia** ☐ Elevation in blood lipid levels ☐ Elevation of blood triglyceride levels **Hypertension** ☐ Elevated blood pressure	**Hyperlipidemia** • Prescribe a statin where appropriate† • Ensure patients and caregivers understand the importance of routine blood tests • Monitor patients' lipid levels **Hypertension** • Start or change hypertension medications‡
MONTH 1-2	**Edema** ☐ Swelling of hands, legs, or feet **CNS** ☐ Mood effects (*eg, anxiety, irritability, depression*)	**Edema** • Suggest compression garments • Recommend increasing exercise • Consider reducing salt intake **CNS** • If bothersome, dose interruption • Dose reduction • Encourage meditation • Suggest cognitive behavioral therapy
MONTH 2-3	**CNS** ☐ Psychotic effects (*eg, hallucinations*)	**CNS** • Dose interruption/reduction • If severe, consider a psychiatrist for pharmacological management
MONTH 3-4	**CNS** ☐ Difficulty speaking ☐ Slow speech ☐ Dysarthria ☐ Cognitive effects **Peripheral neuropathy** ☐ Pain in joints ☐ Numbness and tingling **Weight gain** ☐ Increase in body weight	**CNS** • Dose interruption/reduction • Suggest cognitive behavioral therapy **Peripheral neuropathy** • Suggest raising affected area above heart for pain or numbness • Recommend physiotherapy for pain or numbness • Monitor salt intake • Prescribe vitamins B1 and B6 **Weight gain** • Recommend increasing exercise • Consider food intake counseling or dietary recommendations
MONTH 5-6	**CNS** ☐ Memory impairment	**CNS** • Dose interruption/reduction

*CNS symptoms, blood pressure, cardiovascular function, hyperglycemia, and hyperlipidemia should all be assessed at baseline and then periodically throughout treatment.[1,4]

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