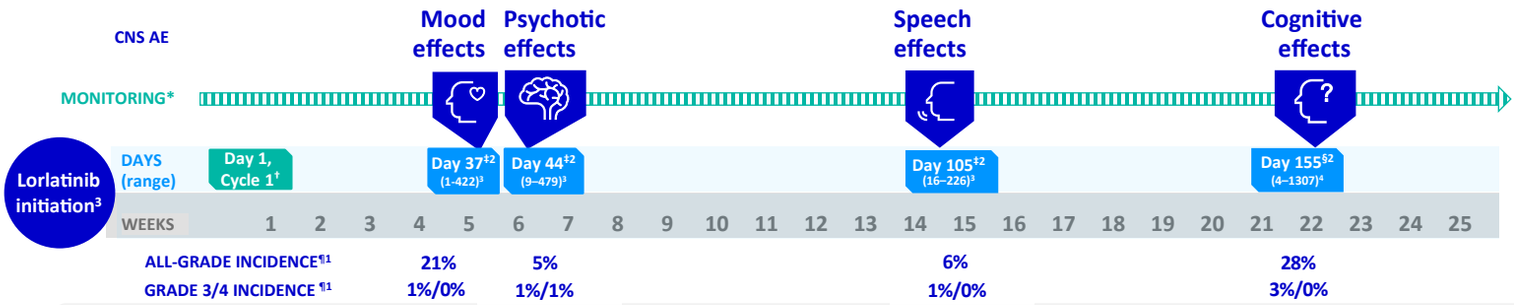
Lorlatinib CNS Adverse Events

Monitoring, Management and Discussion Factsheet

Counsel patients, family and care partners about the possibility of CNS AEs and expectations for monitoring* (at each clinical visit)

The CROWN study reports CNS AEs (cluster term) as **four distinct types of AEs** that can present at various stages during lorlatinib therapy[1]:



In CROWN (5-year analysis), all-causality CNS AEs occurred in **42% of patients**, the majority of which (86%) were of grade 1/2 severity, and 3 out of 149 patients discontinued treatment due to CNS AEs[1]

*At every visit, asking questions regarding memory problems, impaired judgement, changes in mood or interactions with family members and a quick review of the CNS AEs can help trigger early reporting. Brain imaging can be considered in the presence of residual or severe CNS symptoms.[2] †A proper baseline assessment is important: the degree that the patient is affected by the AE is subjective and based on baseline function, daily lifestyle and activities. The greater the degree to which the patient experiences bothersome symptoms and functional detriment, the greater the likelihood that mitigation strategies and/or dose modifications will be needed.[2] ‡CROWN post hoc interim analysis. §CROWN post hoc 3-year analysis. ¶CROWN 5-year analysis.

The following details CNS AE definitions and considerations for patients and their care partners

Type of CNS AE	Definition*[1]	Considerations for these lorlatinib-associated AEs, particularly in patients with†‡[5]:
Cognitive effects	Cognitive and attention disorders and disturbances, deliria (including confusion) or mental impairment disorders	A history of baseline BM, baseline psychiatric illness, previous brain radiation and/or use of psychiatric medications, antiepileptics or stimulants
Mood effects	Anxiety disorders and symptoms, depressed mood disorders and disturbances, manic and bipolar mood disorders and disturbances, mood disorders and disturbances NEC or personality disorders and disturbances in behaviour	A history of pre-existing psychiatric illness, concomitant stimulant use, previous brain surgery, baseline use of psychiatric medications, benzodiazepines or sedatives
Psychotic effects	SMQ narrow psychosis and psychotic disorders or PT of psychotic symptom	A history of previous brain surgery and/or older age [~59 (range 38–85) years]
Speech effects	Speech and language abnormalities	A history of baseline brain radiation and/or concomitant use of antiepileptics

*Per CROWN.[1] †The association of the following patient factors of CNS AEs was reported at different rates in the B7461001 study vs in the real-world setting. Causality has not necessarily been determined, rather the potential impact of factors on CNS AEs.[5] ‡Patients with psychiatric conditions were excluded from enrolling in CROWN.[6]

CNS AEs should primarily be managed with dose modifications

Non-pharmacologic mitigation strategies, including referrals[2]

- Manage other potential causes of neurocognitive and psychiatric issues*
- Refer to a specialist (eg neurologist, psychiatrist)
- Use strategies to minimize CNS AEs: setting reminders, mindfulness, meditation and cognitive behavioural therapy

Pharmacologic mitigation strategies, including medications used in CROWN†

- Lorlatinib early dose interruption and dose reduction[2]
- If severe, refractory CNS AEs occur, consult a psychiatrist for pharmacologic management.[2] In CROWN (post hoc analysis), 13 out of 149 lorlatinib-treated patients (~8.7%) received concomitant medications for CNS AEs,[3,7] which included[7]:
  - **Antidepressants** (duloxetine hydrochloride, escitalopram, escitalopram oxalate, paroxetine hydrochloride, venlafaxine)
  - **Antiepileptics** (clonazepam, levetiracetam, valproate semisodium, valproate sodium)
  - **Antipsychotics** (haloperidol, promazine hydrochloride, quetiapine, quetiapine fumarate, risperidone)
  - **Anxiolytics** (alprazolam, delorazepam, etizolam, lorazepam)
  - **Hypnotics and sedatives** (midazolam, zopiclone)
  - **Psychostimulants/agents for ADHD and nootropics** (clonidine)

*Including development of BM and introduction of any new medications during treatment. †The concomitant medications for CNS AEs used in CROWN are not necessarily recommended pharmacologic agents for every patient and do not include considerations for DDIs.

AE=adverse event; ADHD=attention deficit hyperactivity disorder; BM=brain metastases; CNS=central nervous system; DDI=drug–drug interaction; NEC=not elsewhere classified; PT=preferred term; SMQ=Standardized Medical Dictionary for Regulatory Activities Queries.

1. Solomon BJ, et al. *J Clin Oncol*. 2024;42:3400-3409. Supplementary Appendix. 2. Liu G, et al. *Lung Cancer*. 2024;191:107535. 3. Solomon BJ, et al. *J Clin Oncol*. 2022;40:3593-3602. 4. Solomon BJ, et al. *Lancet Respir Med*. 2023;11:354-366. Supplementary Appendix. 5. Dagogo-Jack I. *J Thorac Oncol*. 2023;18:67-78. 6. Pfizer. CROWN Protocol. 6 December 2022. Protocol No. B7461006. 7. Solomon BJ, et al. *J Clin Oncol*. 2022;40:3593-3602. Supplementary Appendix.

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Accurate grading of lorlatinib AEs, including CNS AEs, is important for management decisions

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CNS AEs*[1]	Mild disturbances without influence on daily activities of life	Moderate disruption affecting daily activities of life	Serious disorders, no hospitalization required	Harm to self or others and/or hospitalization required	Death

*Refer to CTCAE for mood, psychotic, speech and cognitive effect grading definitions.

Lorlatinib doses can be modified. Dose reduction did not seem to impact PFS or IC efficacy[2]

*CROWN post-hoc analysis in patients who had a dose reduction (from 100 mg to 75 mg) within the first 16 weeks.[2,3]

Recommended dose modifications for CNS AEs:

Per SmPC[4]

If grade 2 or 3	If grade 4
Withhold dose	**Permanently discontinue lorlatinib**
After recovery to grade 0 or 1	
Resume lorlatinib At one reduced dose level	

Per the *Pragmatic Guide for Management of Adverse Events Associated with Lorlatinib*[5]

How *bothersome* is the toxicity for the patient?			Reassess (monthly until stable/improved)
Not	**Mildly to moderately**	**Severely**	
Toxicity management (CNS: cognitive, mood, speech, psychotic)	⏸ → – 25 mg	⏸ → – 25 mg	**If worse:** – 25 mg **If stable:** ▶ **If better:**

Legend

- ⏸ **Pause:** lorlatinib dose interruption
- ▶ **Continue:** maintain the same lorlatinib dose
- – 25 mg **Reduce:** lorlatinib dose reduction (by 25 mg decrements)

Discussion guide*

Preparation and counselling of patients and/or their care partners on the potential for CNS AEs are important to support timely recognition and appropriate management

Conducting a baseline assessment and using open-ended questions during ongoing monitoring with your patients and/or their care partners can help uncover changes in symptom burden and severity, which can impact their daily life

Cognitive effects	• Have you noticed any changes in your memory or concentration since starting lorlatinib? If so, could you describe those? • Could you describe any challenges, if any, with finding the right words while speaking? • In what ways, if any, have you noticed changes in the ability to multitask?
Mood effects	• Could you describe any changes in mood you have experienced, if any, such as feeling more anxious, irritable or depressed? • Can you elaborate on any changes in interest or pleasure when doing things, if any? • In what ways, if any, have you noticed trouble concentrating on things, such as reading or watching television?
Psychotic effects	• Could you describe any unusual thoughts, paranoia or hallucinations you may have experienced, if any? • Have you had any strange or odd experiences lately that you cannot explain? If so, can you describe that experience? • How would you describe your interactions with others recently? Have there been any situations that have caused you concern or discomfort?
Speech effects	• Have you noticed any slurring of speech while speaking? If so, can you describe that experience? • Have you noticed any changes to the speed of your speech recently?

*Adapted from Patient Health Questionnaire-2 (PHQ-2), Generalized Anxiety Disorder 2-item (GAD-2) and Psychosis: Screening & Assessment.

AE=adverse event; CNS=central nervous system; CTCAE=Common Terminology Criteria for Adverse Events; IC=intracranial; PFS=progression-free survival; SmPC=Summary of Product Characteristics.

1. Common Terminology Criteria for Adverse Events (CTCAE). V4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf. Accessed: 25 June 2025. 2. Solomon BJ, et al. *J Clin Oncol.* 2024;42:3400-3409. Supplementary Appendix.
3. Pfizer. CROWN Protocol. 6 December 2022. 4. Local Prescribing Document for LORBRIQUA® version 7 Pfizer India _LPDLOR072024
5. Liu G, et al. *Lung Cancer.* 2024;191:107535.

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