Asciminib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) in the chronic phase (CP), who have previously been treated with two or more tyrosine kinase inhibitors (TKIs).	C92	00847	CDS 01/11/2023

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Asciminib is taken orally, twice daily and treatment is continued until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Asciminib	40mg* twice daily	PO	Continuous
* Consideration may be given to the administration of the unlicensed[i] dosing posology of asciminib 80mg once daily at the discretion of the prescribing Consultant.			
The tablets should be taken orally without food. Food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib.			
The film-coated tablets should be swallowed whole with a glass of water and should not be broken, crushed or chewed.			
The tablets should be taken at approximately 12-hour intervals.			
If a dose is missed by less than 6 hours, it should be taken and the next dose should be taken as scheduled. If a dose is missed by more than approximately 6 hours, it should be skipped and the next dose should be taken as scheduled.			

ELIGIBILITY:

- Indication as above
- ECOG status 0-2
- Adequate organ and haematological function

EXCLUSIONS:

- Hypersensitivity to asciminib or to any of the excipients
- Presence of the T315I mutation
- Pregnancy / breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- Magnesium and potassium
- Lipase and amylase
- ECG
- Blood pressure
- Bone marrow examination for cytogenetic analysis
- Analysis by RQ-PCR BCR-ABL transcript level and screening for BCR-ABL kinase– domain mutation
    - Confirmation of the absence of the T315I mutation using a validated test method
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV
  *(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

- FBC every two weeks for the first 3 months, then monthly thereafter or as clinically indicated
- Renal and liver profile
- Blood glucose if clinically indicated
- Magnesium and potassium
- Lipase and amylase
- ECG as clinically indicated and if patients are on other medications that are known to prolong QTc
- Blood pressure
- BCR-ABL transcript analysis every 3 months

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- The starting dose is 40 mg twice daily, while the reduced dose is 20 mg twice daily
- The dose can be modified based on individual safety and tolerability as shown in Tables 1, 2 and 3
- Asciminib should be permanently discontinued in patients unable to tolerate a dose of 20 mg twice daily

Haematological:

Table 1: Dose modification of asciminib in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
< 1.0	**and/or**	**< 50**	Withhold asciminib until resolved to ANC ≥1 x 10^9/L and/or platelets ≥50 x 10^9/L • If resolved within 2 weeks, resume at starting dose • After more than 2 weeks, resume at reduced dose of 20mg twice daily
Recurrent severe thrombocytopenia and/or neutropenia			Withhold asciminib until resolved to ANC ≥1 x 10^9/L and platelets ≥50 x 10^9/L, then resume at reduced dose of 20mg twice daily.

Renal and Hepatic Impairment:

Table 2: Dose modification of asciminib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment.	No dose adjustment is required in patients with mild, moderate or severe hepatic impairment.

Management of adverse events:

Table 3: Dose Modification of asciminib for Adverse Events

Adverse reactions	Recommended dose modification
Asymptomatic amylase and/or lipase elevation Elevation >2.0 x ULN	Withhold asciminib until resolved to <1.5 x ULN • If resolved, resume at reduced dose of 20mg twice daily. If events reoccur at reduced dose, permanently discontinue • If not resolved, permanently discontinue. Perform diagnostic tests to exclude pancreatitis
Grade 3 or higher* non-haematological adverse reactions	Withhold asciminib until resolved to grade 1 or lower • If resolved, resume at reduced dose of 20mg twice daily • If not resolved, permanently discontinue
* Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03.	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low **(Refer to local policy)**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with asciminib and for at least 3 days after stopping treatment.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Asciminib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Myelosuppression**: Treatment with asciminib is associated with thrombocytopenia, neutropenia and anaemia. Severe thrombocytopenia and neutropenia were reported during treatment with asciminib. Myelosuppression was generally reversible and managed by temporarily withholding treatment. Patients should be monitored for signs and symptoms of myelosuppression. Based on the severity of thrombocytopenia and/or neutropenia, the dose should be temporarily withheld, reduced or permanently discontinued as described in Table 1.
- **Pancreatic toxicity**: Pancreatitis and asymptomatic elevations of serum lipase and amylase, including severe reactions, occurred in patients receiving asciminib. Patients should be monitored for signs and symptoms of pancreatic toxicity. More frequent monitoring should be performed in patients with a history of pancreatitis. If serum lipase and amylase elevations are accompanied by abdominal symptoms, treatment should be temporarily withheld and appropriate diagnostic tests should be considered to exclude pancreatitis. Based on the severity of serum lipase and amylase elevations, the dose should be temporarily withheld, reduced or permanently discontinued as described in Table 1.
- **QT prolongation**: QT prolongation occurred in patients receiving asciminib. Hypokalaemia and hypomagnesaemia should be corrected prior to asciminib administration and monitored during treatment as clinically indicated. Caution should be exercised when administering asciminib concomitantly with medicinal products with known risk of torsades de pointes.
- **Hypertension**: Hypertension, including severe hypertension, occurred in patients receiving asciminib. Hypertension and other cardiovascular risk factors should be monitored regularly and managed using the standard therapies during treatment with asciminib.
- **Hepatitis B reactivation**: Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus following administration of other BCR-ABL1 tyrosine kinase inhibitors (TKIs). Patients should be tested for HBV infection before the start of treatment with asciminib. HBV carriers who require treatment with asciminib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy (Refer to local infectious disease policy). These patients should be considered for assessment by hepatology.
- **Lactose**: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

DRUG INTERACTIONS:

- Caution should be exercised during concomitant administration of asciminib and medicinal products with known risk of prolonged QTC and torsades de pointes, including, but not limited to, bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide.

- Caution should be exercised during concomitant administration of asciminib with strong CYP3A4 inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin or St. John's wort (Hypericum perforatum), which may result in lower efficacy of asciminib.
- Caution should be exercised during concomitant administration of asciminib with CYP3A4 substrates known to have a narrow therapeutic index, including, but not limited to, the CYP3A4 substrates fentanyl, alfentanil, dihydroergotamine or ergotamine. Dose adjustment of asciminib is not required.
- Caution should be exercised during concomitant administration of asciminib with CYP2C9 substrates known to have a narrow therapeutic index, including, but not limited to, phenytoin or warfarin. Dose adjustment of asciminib is not required.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. Réa D et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021 Nov 25; 138 (21):2031-2041. doi: 10.1182/blood.2020009984. PMID: 34407542; PMCID: PMC9728405.
3. Breccia M et al. ASC4OPT: A Phase 3b Open-Label Optimization Study of Oral Asciminib in Chronic Myelogenous Leukemia in Chronic Phase Previously Treated with 2 or More Tyrosine Kinase Inhibitors. Blood. 2022 Nov 15 140 (Supplement 1): 9635–9636. https://ashpublications.org/blood/article/140/Supplement%201/9635/487164/ASC4OPT-A-Phase-3b-Open-Label-Optimization-Study
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Asciminib (Scemblix®) film-coated tablets. EMA. Last updated: 02/03/2023. Accessed: 31/07/2023. Available at: https://www.ema.europa.eu/en/documents/product-information/scemblix-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/11/2023		NCCP Myeloid CAG

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed posology for the use of asciminib in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy