DRUG NAME: Momelotinib

SYNONYM(S)[1]: CYT 387, GS-0387, momelotinib dihydrochloride monohydrate

COMMON TRADE NAME(S): OJJAARA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Momelotinib is an orally administered inhibitor of wild type Janus Kinases 1 and 2 (JAK1/JAK2), mutant JAK2^{V617F} and activin A receptor type 1 (ACVR1). JAKs mediate the signaling pathway of cytokines and growth factors for hematopoiesis and immune function. In myelofibrosis, dysregulated JAK signaling leads to impaired hematopoiesis and immune function. By inhibiting the Janus Kinases (JAK1/JAK2), momelotinib blocks downstream signaling, preventing overproduction of cytokines and thereby reducing inflammation. Additionally, momelotinib and its active metabolite M21 inhibit ACVR1, which decreases hepcidin level, resulting in increased iron availability for red blood cell production. Momelotinib and M21 potentially inhibit other JAK family members, inhibitor of κB kinase, and interleukin-1 receptor-associated kinase 1.[2,3]

PHARMACOKINETICS:

Oral Absorption	T_{max}: 2 h; no clinically meaningful effect of food on pharmacokinetics	
Distribution	extensive tissue distribution	
	cross blood brain barrier?	no information found
	volume of distribution	984 L
	plasma protein binding	91%
Metabolism	metabolized by multiple CYP 450 enzymes; CYP 3A4 (36%), CYP 2C8 (19%), CYP 2C19 (19%), CYP 2C9 (17%), CYP 1A2 (9%)	
	active metabolite(s)	M21; created by CYP metabolism followed by aldehyde oxidase metabolism
	inactive metabolite(s)	no information found
Excretion	primarily by fecal elimination	
	urine	28% (12% as M21, <1% as unchanged drug)
	feces	69% (13% as unchanged drug)
	terminal half life	4-8 hr
	clearance	103 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Myeloproliferative neoplasms

Other uses:

*Health Canada approved indication

Developed: 1 October 2025
Revised:

SPECIAL PRECAUTIONS:

Caution:
- starting dose reduction is recommended for patients with severe **hepatic impairment**[2]
- serious and fatal ***infections*** have been reported; do not start momelotinib until active infections have resolved[2]
- ***reactivation of Hepatitis B virus*** (HBV) has been reported with momelotinib[2]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***
- thrombosis, secondary malignancies, and major adverse cardiac events (MACE) are known ***class effects of JAK inhibitors;*** patients with risk factors or prior history of these conditions may be at increased risk of experiencing these events during treatment with momelotinib[2]

Carcinogenicity: Secondary malignancies, including non-melanoma skin cancers, were reported in patients receiving momelotinib in clinical trials,[4] although a causal association in patients has not been established.[2] In animal studies, there was no evidence of tumorigenicity in mice. However, in a 2-year carcinogenicity study in rats, momelotinib caused benign Leydig cell tumours at exposures 17 times higher than the expected human systemic exposure at clinically recommended doses. This increase in Leydig cell adenomas was considered related to a rat-specific phenomenon (i.e., prolactin-dependent Leydig cell tumorigenesis).[2]

Mutagenicity: Not mutagenic in Ames test. Momelotinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: In animal studies, momelotinib impaired fertility in male and female test subjects. In male rats, reduced sperm concentration/motility and decreased testes/seminal vesicle weights were observed at exposures 13 times higher than those expected with clinically recommended doses. Reduced fertility was observed at higher test doses. In female rats, momelotinib reduced ovarian function (reproductive cycles and ovulation) and increased pre- and post-implantation losses were observed, with most pregnant rats experiencing total litter loss at exposures 13 times higher than those expected with clinically recommended doses.[2]

Pregnancy: In animal studies, embryo-fetal toxicity appeared to be dose dependent. When administered during organogenesis in rats, momelotinib did not cause developmental toxicity at exposures equivalent to the clinically recommended dose in humans. However, skeletal variations were observed at exposures 3.5 times higher than those expected with clinically recommended doses. And, at the highest test dose, embryonic death, soft tissue anomalies, skeletal variations, and lower mean fetal body weights were observed. In a development study, decreased pup body weight and embryo lethality were observed in rats at exposures two times higher than those expected with clinically recommended doses. In rabbits, no developmental toxicity was observed at lower test doses. However, when administered during organogenesis at higher test doses, reduced fetal weight, delayed bone ossification, and abortion were observed at exposures less than those expected with clinically recommended doses. Based on the findings from animal studies, momelotinib may cause embryo-fetal toxicity in humans. For female patients of childbearing potential, contraception is recommended during treatment and for at least 1 week after the last dose. However, momelotinib may decrease the effectiveness of hormonal contraceptives. On the basis of *in vitro* studies, momelotinib may induce PXR regulated enzymes (e.g., CYP 1A2, CYP 2B6, and CYP 3A) which may decrease the systemic concentration of hormonal contraceptives and lead to their reduced efficacy.[5] Consider adding a barrier method of contraception for women using hormonal contraceptives.[2,5]

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, momelotinib was detected in nursing pups of treated test subjects. Significantly reduced pup survival and decreased pup body weights were observed at maternal exposures approximately 2 times higher than those expected with clinically recommended doses. These results were considered a direct effect of momelotinib on the pup via exposure through the milk. Women should not breastfeed during treatment and for 1 week after the last dose of momelotinib.[2]

Developed: 1 October 2025
Revised:

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[6,7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (11-15%, severe 10-15%)
	febrile neutropenia (severe 3%)[3]
	leukopenia (14-25%, severe 5%)
	lymphopenia (21-32%, severe 7-11%)
	neutropenia (5%, severe 5%)
	thrombocytopenia (21-28%, severe 11-22%); median onset is 28 days
cardiac	arrhythmia (5-8%, severe 1-2%)
	heart failure (4%)
	cardiovascular events (8%, severe 7%), including cardiovascular death, myocardial infarction, and stroke [4]
eye	blurred vision (3%)
gastrointestinal	*emetogenic potential:* minimal (rare)[8]
	abdominal pain (13-18%, severe 1%)
	diarrhea (20-23%, severe 1%)
	nausea (16-20%, severe 2%)
	vomiting (8%, severe 1%)
general disorders and administration site conditions	fatigue (21-25%, severe 2%)
	syncope (3%)
	peripheral edema (11%)
	pyrexia (10-12%, severe 1-2%)
hepatobiliary	drug induced-liver injury (<1%)
infections and infestations (see paragraph following **Side Effects** table)	***bacterial infection*** (15-21%, severe 8%)
	fungal infection (3%)
	hepatitis B reactivation
	opportunistic infections (6%, severe 2%)[4]
	pneumonia (4-8%, severe 8%)
	urinary tract infection (5-6%, severe 2%)
	viral infection (6-12%, severe 5%); includes COVID-19 (3%)
investigations	***ALT increase*** (15-28%, severe 1%); see paragraph following **Side Effects** table
	AST increase (19-28%); see paragraph following **Side Effects** table

Developed: 1 October 2025
Revised:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	blood bilirubin increase (16%)[9]; see paragraph following **Side Effects** table
	calcium decrease (5-14%, severe 1%)
	creatinine increase (25-36%, severe <1%)
	GGT increase (15-31%, severe 1-4%)
metabolism and nutrition	vitamin B1 deficiency (6%)
musculoskeletal and connective tissue	arthralgia (5%)
	back pain (7%, severe 1%)
	pain in extremity (12%)
neoplasms	non-melanoma skin cancer (5%, severe <1%)[4]
nervous system	dizziness (8-24%, severe 2%); includes vertigo
	headache (11%)
	paresthesia (8%, severe 1%)
	peripheral neuropathy (12%); median onset is 64 days
	polyneuropathy(4%)
renal and urinary	acute kidney injury (3%)
respiratory, thoracic, and mediastinal	cough (8-14%, severe 5%)
	respiratory failure (2%)
skin and subcutaneous tissue	pruritus (11%, severe 2%)
	rash (6-12%); severe cases requiring hospitalization have been reported
	toxic epidermal necrolysis[9]
vascular	flushing (3%)
	hemorrhage (21-22%, severe 2%); includes epistaxis, hematoma, hematuria
	hypotension (14%, severe 2%)
	thromboembolism (9%, severe 5%)[4]; includes deep venous thrombosis and pulmonary embolism

Adapted from standard reference[2] unless specified otherwise.

Infections are reported in 40% of patients treated with momelotinib, with severe cases occurring in 10% of patients. Fatalities have been reported. Median time to onset is 54 days. Reported infections include urinary tract infection, upper respiratory tract infection, pneumonia, nasopharyngitis, COVID-19, cystitis, bronchitis, oral herpes, cellulitis and sepsis.[2,10] Opportunistic infections, such as herpes zoster, fungal infections, and atypical bacteria, have also been reported.[4] Momelotinib treatment should not be started until active infections have resolved. Reactivation of Hepatitis B virus (HBV) has been reported with momelotinib[2]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***.

New or worsening ***elevation of liver enzymes*** is reported with momelotinib. Although rare, reversible drug-induced liver injury has been reported. The median time to onset of transaminase elevation is 2 months, with 75% of cases occurring within 4 months.[9] Starting dose reduction to 150 mg once daily is recommended in patients with pre-existing severe hepatic impairment (Child-Pugh class C). Monitor liver enzymes at baseline and regularly during

Developed: 1 October 2025
Revised:

treatment. Management of hepatoxicity may include treatment interruption and dose reduction. Permanently discontinue momelotinib for recurrence of ALT or AST elevation greater than 5 times the ULN.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
midazolam[5]	no clinically significant changes; 16% decrease in momelotinib AUC and 8% decrease in C_{max}	weak induction of CYP 3A4 by momelotinib	no action required
omeprazole[2]	no clinically meaningful changes; 33% decrease in momelotinib AUC and 36% decrease in C_{max}	pH-dependent solubility	no action required
rosuvastatin[2,9]	220% increase in rosuvastatin AUC and 170% increase in C_{max}	inhibition of BCRP by momelotinib	If concurrent therapy is unavoidable, initiate rosuvastatin at 5 mg and limit rosuvastatin dose to maximum of 10 mg once daily[9]
rifampin[2]	**Inhibition effect** following *single dose* of rifampin: 57% increase in momelotinib AUC and 40% increase in C_{max} **Induction effect** following *multiple doses* of rifampin: 46% decrease in momelotinib AUC and 29% decrease in C_{max} **Net effect** when co-administered with rifampin (600mg daily for 7 days): no significant changes in momelotinib AUC and C_{max}	combined mechanism: inhibition of OATP1B1/1B3 and strong induction of CYP 3A4 by rifampin	no dose modification of momelotinib is required[10]
ritonavir[2]	no clinically significant changes in momelotinib and M21 (active metabolite) pharmacokinetics	strong inhibition of CYP3A4 by ritonavir	no action required

Momelotinib is a *substrate* of CYP 3A4. Strong ***CYP 3A4 inducers*** may decrease the plasma concentration of momelotinib; monitor for decreased momelotinib efficacy.[2] Coadministration of momelotinib with strong ***CYP 3A4 inhibitors*** does not appear to cause clinically significant changes in the pharmacokinetics of momelotinib or its active metabolite, M21.[9]

Momelotinib is a *substrate* of CYP 2C8, CYP 2C9, CYP 2C19, and CYP 1A2; clinical significance is unknown.[2]

Momelotinib is a *substrate* of OATP1B1/1B3 transporter. Coadministration of momelotinib with an ***OATP1B1/1B3 inhibitor*** may increase the plasma concentration of momelotinib. Monitor for momelotinib toxicity and consider momelotinib dose reduction based on adverse reactions.[2]

Momelotinib is an *inhibitor* of ***Breast Cancer Resistance Protein*** (BCRP) and may increase the plasma concentration of BCRP substrates. If coadministration is unavoidable, monitor for toxicity of the substrate. Dose reduction of the substrate may be required.[2]

In vitro, momelotinib and M21 are *substrates* of P-gp, BCRP, and hepatic uptake transporters; clinical significance is unknown.[2]

Momelotinib is an *inducer* of CYP 1A2 and CYP 2B6 and an *inhibitor* of CYP 2B6, P-gp, UGT1A1, UGT1A9, and OCT1. In addition, M21 is an *inducer* of UGT1A1 and an *inhibitor* of MATE1. Clinical significance is unknown.[2]

Developed: 1 October 2025
Revised:

SUPPLY AND STORAGE:

Oral: GlaxoSmithKline Inc. supplies momelotinib as 100 mg, 150 mg, and 200 mg film-coated tablets. Store at room temperature.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral [2,3,11]*:*	200 mg (range 100-200 mg) PO once daily Administer with food or on an empty stomach.
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	eGFR ≥15 mL/min: no adjustment required[2] eGFR <15 mL/min: no information found
Dosage in hepatic failure:	Child-Pugh Class A or B: no adjustment required Child-Pugh Class C: reduce starting dose to 150 mg PO once daily[2]
Dosage in dialysis:	no information found

Children: safety and efficacy have not been established

REFERENCES:

1. UpToDate® Lexidrug (database on the Internet). Momelotinib (Lexi-Drugs). UpToDate Inc. Wolters Kluwer.; Accessed July 2, 2025. Updated June 30, 2025. Available at: http://online.lexi.com
2. GlaxoSmithKline Inc. OJJAARA® product monograph. Mississauga, Ontario; January 29, 2025.
3. Gerds AT, Verstovsek,Srdan, Vannucchi,Alessandro M, Al-Ali HK, et al. Momelotinib versus Danazol in Symptomatic Patients with Anaemia and Myelofibrosis Previously Treated with a JAK Inhibitor (MOMENTUM): an Updated Analysis of an International, Double-blind, Randomised Phase 3 Study. The Lancet Haematology ; 2023;10(9):e735–e746
4. Verstovsek S, Mesa R, Gupta V, et al. Momelotinib Long-term Safety and Survival in Myelofibrosis: Integrated analysis of Phase 3 Randomized Controlled Trials. Blood Advances ; 2023;7(14):3582–3591
5. European Medicines Agency. Committe for Medicinal Products for Human Use (CHMP). Assessment Report - OMJJARA (momelotinib). Amsterdam, The Netherlands; November 9, 2023. http://www.ema.europa.eu/ema/
6. Lynda Foltz MD. BC Cancer Myeloid Tumour Group. Personal communication. September, 2025.
7. Donna Forrest MD. BC Cancer Agency Leukemia/BMT Tumour Group. Personal communication. September 2, 2025.
8. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1 , 2022.
9. GlaxoSmithKline. OJJAARA® full prescribing information. Durham, North Carolina, USA; April 18, 2025.
10. GlaxoSmithKline Trading Services Limited. OMJJARA® Summary of Product Characteristics. Dublin, Ireland; May 12, 2025.
11. Mesa RA, Kiladjian J, Catalano JV, et al. SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis. Journal of Clinical Oncology ; 2017;35(34):3844–3850

Developed: 1 October 2025
Revised: