Impact of Concomitant Metamizole on Quizartinib Exposure in QuANTUM-First Study

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PURPOSE

Strong or moderate cytochrome P450 3A (CYP3A) inducers decrease quizartinib exposure and may reduce its efficacy; therefore, concomitant use should be avoided. Metamizole is classified as a moderate inducer in some literature sources, but as a weak inducer in its package insert, leading to its use alongside quizartinib in certain countries. This study assessed metamizole effects on quizartinib pharmacokinetics (PK), efficacy, and safety in the phase 3 QuANTUM-First (QF) trial.

RESULTS

A case study reported that intensive metamizole use substantially reduced exposures of quizartinib and its primary active metabolite, AC886, by more than 60%. However, the QF study observed a decrease of less than 20%, possibly because of lower metamizole intensity. Patients who used metamizole reported shorter response durations and numerically higher rates of early infection and early death in both placebo and quizartinib treatment arms.

CONCLUSIONS

Clinical observations indicate that metamizole – considered a moderate CYP3A inducer – should be avoided in patients receiving quizartinib. Caution is advised when using CYP3A substrates in regions where metamizole is commonly prescribed.

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BACKGROUND

- Quizartinib is a selective oral FMS-related tyrosine kinase 3 (FLT3) inhibitor currently approved in 37 countries and marketed in 11 countries worldwide (as of June 2025) for the treatment of newly diagnosed *FLT3*-internal tandem duplication (ITD)+ acute myeloid leukemia (AML),[1] and for relapsed or refractory *FLT3*-ITD+ AML in Japan[2]
- Quizartinib is metabolized primarily by CYP3A4/5 to its active metabolite AC886, which is also a CYP3A4/5 substrate[1]
- The use of strong or moderate CYP3A inducers with quizartinib should be avoided, as both quizartinib and AC886 exposures are highly sensitive to CYP3A inducers[1]
  - Concomitant administration of efavirenz, a moderate CYP3A inducer, has been shown to reduce the area under the plasma concentration–time curve (AUC) of quizartinib and AC886 by 90% and 96%, respectively, and decrease the maximum plasma concentrations (C_{max}) by 45% and 68%, respectively[1]
- Metamizole, also known as dipyrone, is a non-steroidal anti-inflammatory drug used commonly as an analgesic, antipyretic, or antispasmodic in many countries of Central and South America, Europe, and Asia
  - Metamizole is available in various dosage and administration forms (as prescription only or over the counter)[3–5]

Route	Typical dose	Frequency	Notes
Oral (tablet)	500–1000 mg per dose	Every 6–8 hours as needed (TID–QID)	Maximum daily dose of 4000 mg Use lowest effective dose
Intravenous or intramuscular (injectable solution)	500–1000 mg per dose (usually 1 g)	Every 8 hours as needed (up to QID)	
Rectal (suppository)	1000 mg per suppository	Every 6–8 hours as needed (up to QID)	

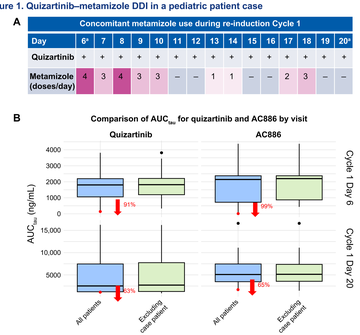
QID, four times daily; TID, three times daily.

- Metamizole is unavailable in the USA, Canada, or the UK due to the potential for the very rare side effect of agranulocytosis – a sudden drop in white blood cells (< 1 per million daily doses)[3] – and, in June 2024, the European Medicines Agency initiated a review of metamizole because of this risk, which can lead to serious infections[6]
- Considering the reduced global availability, metamizole is often omitted in the drug–drug interaction (DDI) literature[7,8]
  - Although it is reported as a moderate CYP3A inducer in the literature,[4,9,10] metamizole is described as a weak inducer in its package insert,[11] resulting in the concomitant use of quizartinib and metamizole in some countries
- QF (NCT02668653) is a pivotal, global, phase 3, placebo-controlled, clinical trial of quizartinib in newly diagnosed *FLT3*-ITD+ AML,[12] which supported the approval of quizartinib in multiple countries, including those where metamizole is available
  - In the QF study, quizartinib was administered as an add-on regimen to a standard chemotherapy backbone during induction and consolidation phases, and as monotherapy during the maintenance phase

Case report: quizartinib–metamizole DDI in a pediatric patient

- A 12-year-old male with refractory AML who received concomitant metamizole exhibited a substantial decrease in quizartinib and AC886 exposures on Day 6 (the first day of quizartinib administration) and at steady state (Day 20), consistent with the findings from the efavirenz (a moderate CYP3A inducer) DDI study (data on file)
  - The patient was receiving metamizole 1480 mg up to four times daily as needed, to alleviate fever or pain (**Figure 1A**)
  - On Day 6, the AUCs of quizartinib and AC886 were 91% and 99% lower, respectively, compared with the overall population; at steady-state, exposures were reduced by 63% and 65%, respectively (**Figure 1B**)

Figure 1. Quizartinib–metamizole DDI in a pediatric patient case



*PK samples were collected on re-induction Cycle 1, on the 1st (Day 6) and the 15th (Day 20) day of administration of quizartinib.
Box plot in blue shows all patients, red dots represent the data for the case patient; box plot in green shows sensitivity test result excluding the case patient.
AUC, area under the plasma concentration–time curve; DDI, drug–drug interaction; PK, pharmacokinetics.

OBJECTIVE

- The concomitant use of strong or moderate CYP3A inducers with quizartinib decreases its systemic exposure and may reduce efficacy; therefore, such combinations should be avoided, as recommended in the prescribing information
- Although metamizole is classified as a moderate CYP3A inducer in the literature, it is listed as a weak inducer in its package insert, resulting in its concomitant use with quizartinib in some countries
- Here, we evaluated the use of metamizole in the QF study and its impact on quizartinib PK, efficacy, and safety

METHODS

- The analyses included patients from the QF study (data cutoff August 13, 2021)
  - Patients with ≥ 1 use of metamizole while receiving quizartinib or placebo were considered as having concomitant metamizole use
  - For metamizole users in both quizartinib and placebo arms, durations and utilizations of metamizole by treatment phases were calculated using the start and end dates of metamizole use, regardless of dosing frequency
    - Metamizole utilization rate (%) = (days of concomitant metamizole use/days of the phase) × 100
- Phase-specific C_{max} and AUC, predicted from the population PK (PopPK) analysis, were used for post hoc comparison of PK metrics by metamizole use and treatment phases
- The PK concentration versus time was plotted using observed PK data points, with locally weighted scatterplot smoothing (LOWESS) curves applied to illustrate overall trends (**Figure 2**)
- Efficacy analyses included the intent-to-treat population
  - Overall survival (OS), defined as time from randomization until death from any cause, was the primary outcome
  - Complete remission/composite complete remission (CR/CRc) rate during the induction phase, and duration of CR (DOCR)/duration of CRc were evaluated as exploratory endpoints
- Safety graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events was assessed in all patients who received ≥ 1 dose of quizartinib or placebo plus ≥ 1 use of metamizole
  - Treatment-emergent adverse event (TEAE) rates during the induction phase, and early death and early infection rates within the first 30 and 60 days were assessed

RESULTS

Patient demographics, baseline characteristics, and metamizole use

- Patients had a median age of 56 years (range 20–75), with similar numbers of females and males, and were mostly white (59.7%) (**Table 1**)
  - Most patients using metamizole were white, and its use was slightly higher among quizartinib-treated patients with an Eastern Cooperative Oncology Group performance status score of 2
- Metamizole was used in 22.9% of patients (n = 122; 66 in the quizartinib arm and 56 in the placebo arm) enrolled in the QF study, primarily during the induction and consolidation phases (**Table 2**)
  - Overall, metamizole was used for a median of 10.5 days in the quizartinib arm and 7 days in the placebo arm
  - The median overall metamizole utilization rates were 4.5% and 4.8% among patients in the quizartinib and placebo arms, respectively

Table 1. Patient demographics and characteristics at baseline

Parameter	Metamizole use (n = 122)		No metamizole use (n = 411)		Total (N = 533)
	Quizartinib (n = 66)	Placebo (n = 56)	Quizartinib (n = 199)	Placebo (n = 212)	
Age					
Median (range), years	56.5 (23, 72)	54.5 (23, 73)	55 (23, 75)	56 (20, 75)	56 (20, 75)
< 60 years	40 (60.6)	35 (62.5)	119 (59.8)	125 (59.0)	319 (59.8)
≥ 60 years	26 (39.4)	21 (37.5)	80 (40.2)	87 (41.0)	214 (40.2)
< 65 years	12 (18.2)	6 (10.7)	25 (12.6)	37 (17.5)	80 (15.0)
≥ 65 years	14 (21.2)	15 (26.8)	55 (27.6)	50 (23.6)	134 (25.1)
Male, n (%)	33 (50.0)	23 (41.1)	91 (45.7)	97 (45.8)	244 (45.8)
Region, n (%)					
North America	0	0	16 (8.0)	18 (8.5)	34 (6.4)
Europe	61 (92.4)	53 (94.6)	100 (50.3)	108 (50.9)	322 (60.4)
Asia or other regions	5 (7.6)	3 (5.4)	83 (41.7)	86 (40.6)	177 (33.2)
Race, n (%)					
White	64 (97.0)	52 (92.9)	93 (46.7)	109 (51.4)	318 (59.7)
Asian	0	2 (3.6)	79 (39.7)	75 (35.4)	156 (29.3)
Black or African American	0	1 (1.8)	2 (1.0)	4 (1.9)	7 (1.3)
American Indian or Alaska Native	0	1 (1.8)	0	0	1 (0.2)
Other	2 (3.0)	0	25 (12.6)	24 (11.3)	51 (9.6)
ECOG PS score, n (%)					
0	22 (33.3)	22 (39.3)	65 (32.7)	75 (35.4)	184 (34.5)
1	31 (47.0)	26 (46.4)	102 (51.3)	108 (50.9)	267 (50.1)
2	13 (19.7)	8 (14.3)	32 (16.1)	28 (13.2)	81 (15.2)
Missing	0	0	0	1 (0.5)	1 (0.2)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Use of metamizole in QuANTUM-First

Phase	Number of patients using metamizole, n/N (%)		Days of metamizole use median (range), days		Metamizole utilization rate median (range), %	
	Quizartinib	Placebo	Quizartinib	Placebo	Quizartinib	Placebo
Overall	66/265 (24.9)	56/268 (20.9)	10.5 (1–182)	7 (1–317)	4.5 (0.1–100)	4.8 (0.2–100)
Induction	48/265 (18.1)	50/268 (18.7)	7 (1–61)	5 (1–42)	16.3 (0.9–100)	12.5 (0.8–100)
Consolidation	35/173 (20.2)	25/175 (14.3)	5 (1–108)	6 (1–145)	4.3 (0.4–53.3)	5.5 (0.5–8.71)
Maintenance	7/116 (6.0)	7/92 (7.6)	14 (1–74)	2 (1–308)	4 (0.2–100)	2.5 (0.3–52.0)

Post hoc PK comparison

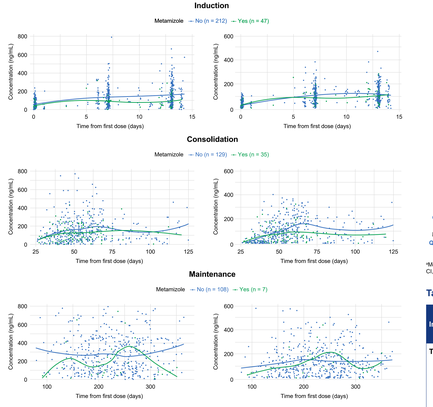
- The PopPK analysis included 259 patients from the QF study (65 metamizole users, and 194 non-users)
- Quizartinib AUCs at steady state (AUC_{ss}) were approximately 20%, 15%, and 5% lower in patients receiving concomitant metamizole during the induction, consolidation, and maintenance phases, respectively (**Table 3**)
- AC886 AUC_{ss} were approximately 12%, 12%, and 33% lower in patients receiving concomitant metamizole during the induction, consolidation, and maintenance phases, respectively (**Table 3**)

Table 3. Quizartinib and AC886 PK summary by phase and metamizole use

	Phase	Quizartinib dose, mg	Metamizole use			No metamizole use			Ratios
			n	AUC, GM (CV%), ng·h/mL	C_{max}, GM (CV%), ng/mL	n	AUC, GM (CV%), ng·h/mL	C_{max}, GM (CV%), ng/mL	AUC GMR
Quizartinib	Induction	40	47	2220 (62.0)	117 (50.4)	212	2790 (89.1)	145 (74.6)	0.798
	Consolidation	40	35	3480 (53.5)	179 (46.5)	129	4070 (83.5)	211 (67.1)	0.854
	Maintenance	60	7	9710 (51.3)	473 (43.3)	108	10,200 (76.3)	532 (60.8)	0.953
AC886	Induction	40	47	3230 (48.2)	148 (50.4)	212	3680 (51.4)	166 (52.1)	0.879
	Consolidation	40	35	3440 (46.2)	156 (47.6)	129	3900 (45.5)	176 (46.8)	0.880
	Maintenance	60	7	3940 (70.0)	175 (73.6)	108	5930 (43.4)	269 (45.1)	0.665

AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; GM, geometric mean; GMR, geometric mean ratio; PK, pharmacokinetics.

Figure 2. Quizartinib (left) and AC886 (right) concentration versus time plots by phase and metamizole use



Lines represent LOWESS curve.
LOWESS, locally weighted scatterplot smoothing.

Efficacy

- Although CR rates were comparable in the quizartinib arm regardless of concomitant metamizole use, metamizole users in the quizartinib arm experienced a numerically shorter DOCR compared with metamizole non-users (22.7 vs 47.7 months) (**Table 4**)
- Lower CRc rates and shorter durations of response were observed in metamizole users, regardless of whether patients received quizartinib or placebo, than non-users (**Table 4**)

Table 4. Rates of CR and DOCR after induction treatment

	Metamizole use		No metamizole use	
	Quizartinib (n = 48)	Placebo (n = 50)	Quizartinib (n = 220)	Placebo (n = 221)
CR rate, n (%)	27 (56.3)	23 (46.0)	120 (54.5)	127 (57.5)
95% CI	41.18–70.52	31.81–60.68	47.72–61.25	50.66–64.07
DOCR, median (95% CI), months	22.7 (13.7–NE)	21.6 (8.8–NE)	47.7 (24.9–NE)	12.4 (6.6–22.7)
CRc (CR + CRi) rate, n (%)	31 (64.6)	30 (60.0)	161 (73.2)	146 (66.1)
95% CI	49.46–77.84	45.18–73.59	66.81–78.91	59.41–72.28
DOCRc, median (95% CI), months	19.9 (13.7–NE)	10.6 (7.7–NE)	28.5 (17.4–NE)	12.4 (7.6–22.8)

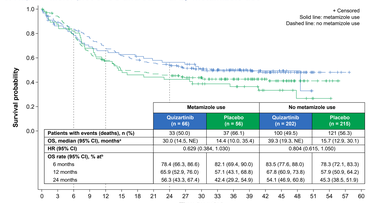
CI, confidence interval; CR, complete response; CRc, composite CR; CRi, CR with incomplete count recovery; DOCR, duration of CR; DOCRc, duration of CRc; NE, not estimable.

- In the quizartinib arm, metamizole users had a numerically lower median OS compared with patients who did not use metamizole (30.0 vs 39.3 months, respectively) (**Figure 3**)
- A trend toward lower OS rates up to 12 months was observed in metamizole users compared with non-users treated with quizartinib

Safety

- Early study-drug TEAE and serious adverse event rates in the induction phase were generally similar across the groups of metamizole users versus non-users in the quizartinib arm (**Table 5**)
  - A higher number of TEAEs associated with death as an outcome was observed among metamizole users versus non-users
- Numerically higher early infection rates within 30 and 60 days (11.3 and 17 percentage points higher, respectively) were observed in metamizole users versus non-users in the quizartinib arm (**Table 6**)
  - Most common infections were pneumonia, sepsis, and oral herpes
- Early death rate within 30 days of treatment initiation was 7.4 percentage points higher among metamizole users than non-users in the quizartinib arm (**Table 7**)
  - Primary reason of death was due to adverse events

Figure 3. Kaplan–Meier plot of OS and survival by metamizole use



	Metamizole use		No metamizole use	
	Quizartinib (n = 66)	Placebo (n = 56)	Quizartinib (n = 202)	Placebo (n = 215)
Patients with events (deaths), n (%)	33 (50.0)	37 (66.1)	100 (49.5)	121 (56.3)
OS, median (95% CI), months[a]	30.0 (14.5, NE)	14.4 (10.0, 35.4)	39.3 (19.3, NE)	15.7 (12.9, 30.1)
HR (95% CI)	0.629 (0.384, 1.030)		0.804 (0.615, 1.050)	
OS rate (95% CI), % at[a]				
6 months	78.4 (66.3, 86.6)	82.1 (69.4, 90.0)	83.5 (77.6, 88.0)	78.3 (72.1, 83.3)
12 months	65.9 (52.9, 76.0)	57.1 (43.1, 68.8)	67.8 (60.6, 73.8)	57.9 (50.9, 64.2)
24 months	56.3 (43.3, 67.4)	42.4 (29.2, 54.9)	54.1 (46.9, 60.8)	45.3 (38.5, 51.9)

No. of patients at risk

Metamizole use																								
Quizartinib (n = 66)	66	55	50	44	42	40	38	36	35	34	27	24	21	17	10	7	3	0						
Placebo (n = 56)	56	49	46	38	31	27	25	24	23	23	19	17	16	13	8	7	4	1	1	0				
No metamizole use																								
Quizartinib (n = 202)	202	178	166	151	134	122	115	109	104	92	83	72	62	51	43	29	21	8	4	1	0			
Placebo (n = 215)	215	200	165	137	120	104	101	97	94	80	72	64	54	43	31	24	13	7	4	0				

[a]Median OS is from Kaplan–Meier analysis. CI for median is computed using the Brookmeyer–Crowley method. [b]Estimated using the Kaplan–Meier method.
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Table 5. Summary of TEAE and SAE during the induction phase

Induction phase	Metamizole use		No metamizole use	
	Quizartinib (n = 48)	Placebo (n = 50)	Quizartinib (n = 217)	Placebo (n = 216)
TEAE, n (%)	48 (100)	49 (98.0)	212 (97.7)	212 (97.2)
TEAE with CTCAE Grade 3	24 (50.0)	21 (42.0)	102 (47.0)	105 (48.2)
TEAE with CTCAE Grade 4	5 (10.4)	13 (26.0)	37 (17.1)	48 (22.0)
TEAE with CTCAE Grade ≥ 3 (including 5*)	36 (75.0)	39 (78.0)	151 (69.6)	161 (73.9)
TEAE associated with death as outcome	7 (14.6)	5 (10.0)	12 (5.5)	8 (3.7)
TEAE associated with treatment discontinuation	6 (12.5)	4 (8.0)	20 (9.2)	7 (3.2)
TEAE associated with dose interruption	5 (10.4)	8 (16.0)	19 (8.8)	22 (10.1)
TEAE associated with dose reduction	1 (2.1)	0	6 (2.8)	3 (1.4)
Treatment-related TEAE, n (%)	15 (31.3)	15 (30.0)	87 (40.1)	62 (28.4)
SAE, n (%)	15 (31.3)	17 (34.0)	60 (27.6)	49 (22.5)
Treatment-related SAE, n (%)	2 (4.2)	3 (6.0)	19 (8.8)	11 (5.0)

*Grade 5 = death related to AE.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious AE; TEAE, treatment-emergent AE.

Table 6. Safety summary of early infections (within 30 days and 60 days)

System Organ Class Preferred Term	Metamizole use within 30 days		No metamizole use within 30 days		Total (N = 533)
	Quizartinib (n = 42)	Placebo (n = 48)	Quizartinib (n = 223)	Placebo (n = 220)	
Within 30 days, n (%)					
Infections and infestations	23 (54.8)	19 (39.6)	97 (43.5)	90 (40.9)	229 (43.0)
Pneumonia	4 (9.5)	4 (8.3)	14 (6.3)	21 (9.5)	43 (8.1)
Sepsis	1 (2.4)	3 (6.3)	5 (2.2)	15 (6.8)	24 (4.5)
Oral herpes	2 (4.8)	1 (2.1)	5 (2.2)	4 (1.8)	12 (2.3)
System Organ Class Preferred Term	**Metamizole use within 60 days**		**No metamizole use within 30 days**		**Total (N = 533)**
	Quizartinib (n = 55)	**Placebo (n = 54)**	**Quizartinib (n = 210)**	**Placebo (n = 214)**	
Within 60 days, n (%)					
Infections and infestations	40 (72.7)	29 (53.7)	117 (55.7)	113 (52.8)	299 (56.1)
Pneumonia	10 (18.2)	6 (11.1)	17 (8.1)	25 (11.7)	58 (10.9)
Sepsis	5 (9.1)	4 (7.4)	6 (2.9)	18 (8.4)	33 (6.2)
Oral herpes	3 (5.5)	2 (3.7)	6 (2.9)	6 (2.8)	17 (3.2)
Cellulitis	0	3 (5.6)	5 (2.4)	6 (2.8)	14 (2.6)
Septic shock	3 (5.5)	2 (3.7)	6 (2.9)	3 (1.4)	14 (2.6)
Bacteremia	2 (3.6)	0	7 (3.3)	3 (1.4)	12 (2.3)
Oral candidiasis	3 (5.5)	1 (1.9)	4 (1.9)	4 (1.9)	12 (2.3)
Sinusitis	4 (7.3)	0	4 (1.9)	4 (1.9)	12 (2.3)
Conjunctivitis	5 (9.1)	3 (5.6)	2 (1.0)	1 (0.5)	11 (2.1)
Staphylococcal infection	2 (3.6)	2 (3.7)	3 (1.4)	4 (1.9)	11 (2.1)

Table 7. Safety summary of early deaths within 30 days

	Metamizole use within 30 days		No metamizole use within 30 days		Total (N = 533)
	Quizartinib (n = 42)	Placebo (n = 48)	Quizartinib (n = 223)	Placebo (n = 220)	
Total number of deaths, n (%)	21 (50.0)	30 (62.5)	109 (48.9)	126 (57.3)	286 (53.7)
Deaths within 30 days of treatment initiation with quizartinib, n (%)	5 (11.9)	3 (6.3)	10 (4.5)	6 (2.7)	24 (4.5)
Primary reason of death within 30 days of treatment initiation with quizartinib, n (%)					
AML disease progression	0	0	0	1 (0.5)	1 (0.2)
TEAE	5 (11.9)	3 (6.3)	9 (4.0)	5 (2.3)	22 (4.1)
Other	0	0	1 (0.4)	0	1 (0.2)

AML, acute myeloid leukemia; TEAE, treatment-emergent adverse event.

DISCUSSION

- The substantial PK reduction reported in the pediatric case study was not observed in the QF study, possibly due to differences in metamizole dosing intensity
  - Additionally, the post hoc PopPK analysis may lack the sensitivity to detect transient PK reductions during treatment
- As noted in the literature, metamizole is a moderate inducer of CYP3A4, CYP2B6, and CYP2C19,[7,8] and high-intensity use of metamizole may decrease exposures of other supportive medications used in AML, such as dexamethasone, or infection-preventing agents like antifungals (eg, posaconazole, voriconazole), which are also CYP3A substrates
- Higher early infection rates observed in metamizole users compared with non-users may be explained by 2 factors:
  - Metamizole is more likely to be administered to patients with persistent fever, creating an association between high-intensity metamizole use and infection
  - Metamizole may reduce systemic exposure to anti-infective medications, as many of these agents are CYP substrates
- Interpretation of metamizole's efficacy and safety is confounded by the limited sample size, regional variations in the standard of care influencing metamizole use, and inconsistencies in its dosing and frequency; therefore, cautious interpretation of these findings is warranted
- Due to the limited data available, the analysis was based solely on the use of metamizole, without accounting for dosage and number of doses per day
  - Future analyses may explore subgroups based on metamizole dosing intensity, such as high-intensity use (eg, 4 g daily for more than 3 days) versus occasional dosing
  - In addition, future analysis may try to promote balance between metamizole users/non-users in terms of baseline characteristics such as regions and risk status

CONCLUSIONS

- Clinical observations indicate that metamizole should be avoided in patients receiving quizartinib
- Precaution should be exercised when using CYP3A substrates in regions where metamizole is commonly prescribed

REFERENCES

1. VANFLYTA® (quizartinib) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; July 2023.
2. Daiichi Sankyo. Press Release. https://www.daiichisankyo.com/media/press_release/detail/index_3180.html. Published June 18, 2019. Accessed July 20, 2025.
3. Brinkman DJ, et al. *Br J Clin Pharmacol* 2025;91:2095–2102.
4. Metamizole [Dipyrone]. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. https://www.ncbi.nlm.nih.gov/books/NBK504194/. Updated June 2, 2024.
5. European Medicines Agency. Metamizole Article 31 referral — Annex III: Amendments to relevant sections of the Product Information. EMEA/H/A-31/1469. https://www.ema.europa.eu/en/documents/referral/metamizole-article-31-referral-annex-iii_en.pdf. Published December 12, 2018. Updated March 28, 2019. Accessed July 20, 2025.
6. European Medicines Agency. Review of painkiller metamizole started. https://www.ema.europa.eu/en/news/review-painkiller-metamizole-started. Published June 14, 2024. Accessed July 20, 2025.
7. US Food and Drug Administration. FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems (Table 1: CYP Enzyme- and Transporter System-Based Clinical Substrates, Inhibitors, or Inducers). https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems. Updated June 27, 2025. Accessed July 2025.
8. Flockhart DA. Drug Interactions Flockhart Table™. Indiana University. https://drug-interactions.medicine.iu.edu/MainTable.aspx. Accessed July 20, 2025.
9. Bachmann F, et al. *Clin Pharmacol Ther* 2021;109:1505–1516.
10. Certara. DDI Marker Studies Knowledgebase. https://www.drug-interactionsolutions.org/blog/ddi-marker-studies-knowledgebase-quarterly-update-111. Updated April 2025.
11. PLM Latinoamérica. NEO-MELUBRINA Jarabe. https://www.medicamentosplm.com/Home/productos/neomelubrina.jarabe/162/101/8841/94. Accessed July 20, 2025.
12. Erba HP, et al. *Lancet* 2023;401:1571–1583.

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