First-generation Gepants Were Discontinued Due To Liver Toxicity, A Concern Not Seen With Second-generation Gepants

Medication	AST or ALT ≥3 X ULN	Assessment on relationship to treatment	Hy's law cases
Atogepant (ADVANCE)[1] (n = 744; 52 weeks)	0.7% atogepant (all groups combined) 1.8% placebo	2, possibly related	None
Rimegepant (Study 201)[2] (n = 1800; 52 weeks)	1.0% not stated	None related	None
Ubrogepant (ACHIEVE 1 and 2)[3] (n = 1230; 52 weeks)	1.3% ubrogepant 50 mg 2.7% ubrogepant 100 mg 1.0% usual care	16 in ubrogepant groups: 13 unlikely related; 2 possibly related; 1 probably related 4 in usual care group	No confirmed cases
Zavegepant[4] (n = 608; 52 weeks)	2.6% not stated	No data	No data

Note: Hy's Law is used to predict acute liver failure in patients with drug-induced liver injury.[5]

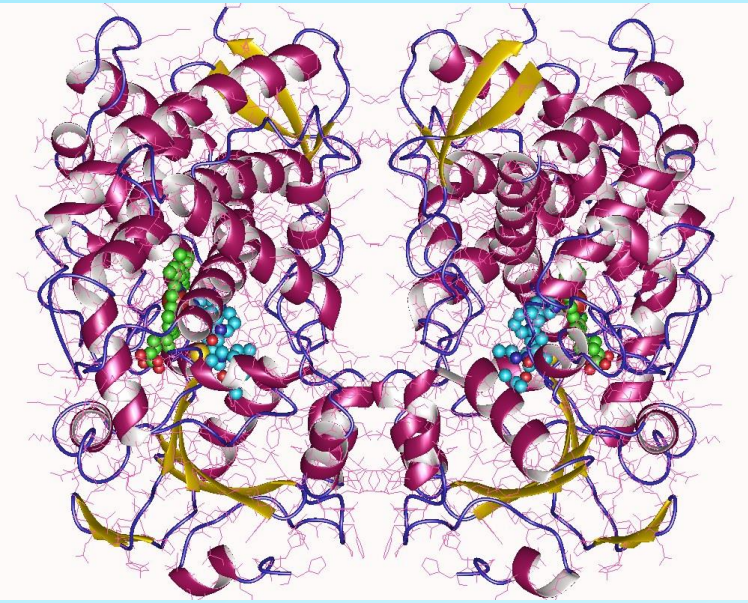
Gepants[6,7,8,9]

- Avoid use or modify dose as directed in patients with severe hepatic impairment

ALT, alanine aminotransferase; AST, aspartate transaminase; ULN, upper limit of normal.

1. Ailani J, et al. *N Engl J Med.* 2021;385(8):695-706; 2. Croop R, et al. *Neurology.* 2020;94(15_supplement):4829; 3. Ailani J, et al. *Headache*. 2020;60(1):141-52; 4. Croop R, et al. *Neurology.* 2023;100(17_supplement_2); 5. Regev A. *Gastroenterology.* 2014;147(1):20-24; 6. Qulipta. Package insert. AbbVie; 2023; 7. Nurtec ODT. Package insert. Pfizer Inc.; 2023; 8. Zavzpret. Package insert. Pfizer Inc.; 2023; 9. Ubrelvy. Package insert. AbbVie Inc.; 2023.

Gepants Require Dosage Adjustments for CYP3A4 Drug Interactions



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Cytochrome P450 3A4 is an important enzyme in the body, mainly in the liver and the intestine

Drug	Drug interactions and dosage adjustments
Atogepant[1] (10 mg, 30 mg, 60 mg doses; max dose 60 mg)	• Strong CYP3A4 inhibitors: 10 mg once daily for EM; avoid use in CM • Strong/moderate/weak CYP3A4 inducers: 30 mg or 60 mg once daily for EM; avoid use in CM
Rimegepant[2] (75 mg dose; max dose 75 mg)	• Strong CYP3A4 inhibitors: avoid concomitant administration • Moderate CYP3A4 inhibitors: avoid another dose within 48 hours when administered with a moderate CYP3A4 inhibitor • Strong/moderate CYP3A inducers: avoid concomitant administration
Ubrogepant[3] (50 mg and 100 mg doses; max dose 200 mg)	• Strong CYP3A4 inhibitors: avoid concomitant administration • Moderate/weak inhibitors: 50 mg • Weak/moderate CYP3A4 inducers: 100 mg
Zavegepant[4] (10 mg dose; max dose 10 mg)	• None listed

Examples:
CYP3A4 inhibitors: itraconazole, ketoconazole, clarithromycin, grapefruit
CYP3A4 inducers: carbamazepine, rifampin, St. John's wort

CM, chronic migraine; EM, episodic migraine.

1. Qulipta. Package insert. AbbVie; 2023; 2. Nurtec ODT. Package insert. Pfizer Inc.; 2023; 3. Ubrelvy. Package insert. AbbVie Inc.; 2023;
4. Zavzpret. Package insert. Pfizer Inc.; 2023.

No Difference Was Found in Safety Concerns Between Cardiovascular Risk Groups

Ubrogepant[1] (ACHIEVE I and ACHIEVE II pooled data)

	No CV risk (58%)		Low CV risk (32%)		Moderate/high CV risk (11%)	
AE within 30 days after treatment	Placebo (n = 549)	Ubro 50 mg (n = 554)	Placebo (n = 335)	Ubro 50 mg (n = 300)	Placebo (n = 100)	Ubro 50 mg (n = 100)
Treatment--related TEAE	8.4%	10.1%	9.3%	6.7%	11.0%	14.0%
SAE	0	0.5%	0	0	0	0

Ubrogepant safety and efficacy for the acute treatment of migraine does not vary with the level of CV risk defined by the presence of major CV risk factors. The adverse event profile of ubrogepant was similar across CV risk categories and was similar to placebo.

Rimegepant open-label safety study (1995)

Trial design	multicenter, long-term, open-label safety study
Participants	1800 adults , history of 2-14 monthly migraine attacks, took rimegepant 75 mg up to once daily for 52 weeks
Subgroups	CV risk factors • none: 59.2% • 1: 28.8% • 2: 12.8% Framingham 10-year risk of developing CV condition • Low: 93% • Moderate to high: 7%
Serious AEs	• 2.3% to 2.7% across CV risk factor groups • 2.4% to 2.6% among those with moderate to high 10-year CV risk • None rimegepant related

The safety and efficacy of gepants did not differ in groups with increased cardiovascular risk factors when using a gepant for acute or preventative migraine treatment.[1,2]

CV, cardiovascular; SAE, serious adverse event; TEAE, treatment emergent adverse event; Ubro, ubrogepant.

1. Hutchinson S, et al. *Cephalalgia.* 2021;41(9):979-90; 2. Hutchinson S, et al. *Neurology.* 2021;96(15_supplement).

Gepants Are Primarily Eliminated by Metabolism, Renal Excretion Percentage Is Low

	Renal excretion (%)	Recommended dose (for prevention)	Maximum daily dose	Mild-to-moderate renal disease	Severe renal disease	End-stage renal disease
Atogepant[1]	5%	10 mg, 30 mg, 60 mg QD	60 mg QD	No dosage adjustment	Limit to 10 mg daily dose (EM); avoid use in CM	Limit to 10 mg daily dose (EM), avoid use in CM
Rimegepant[2]	24%	75 mg QOD	75 mg QD	No dosage adjustment	No dosage adjustment	Not studied
Urogepant[3]	6%	50 mg or 100 mg QD	200 mg QD	No dosage adjustment	50 mg, repeat 50 mg if needed	Avoid use
Zavegepant[4]	11%	10 mg QD	10 mg QD	No dosage adjustment	Avoid use	Avoid use

CM, chronic migraine; EM, episodic migraine; NA, not available; QD, once daily; QOD, every other day.

1. Qulipta. Package insert. AbbVie 2023; 2. Nurtec ODT. Package insert. Pfizer Inc.; 2023; 3. Ubrelvy. Package insert. AbbVie Inc.; 2023;
4. Zavzpret. Package insert. Pfizer Inc.; 2023.