PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}UBRELVY®

Ubrogepant tablets

Tablets, 50 mg and 100 mg, Oral

Calcitonin gene-related peptide (CGRP) receptor antagonist

Migraine Therapy

AbbVie Corporation,
8401 Trans-Canada Highway
Saint-Laurent, Quebec
H4S 1Z1

Date of Initial Authorization:
November 10, 2022

Submission Control Number: 256191

RECENT MAJOR LABEL CHANGES

None at the time of authorization

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

UBRELVY® (ubrogepant tablet) is indicated for the acute treatment of migraine, with or without aura, in adults.

1.1 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Clinical studies of UBRELVY did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Caution should be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions in this population (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics).

2 CONTRAINDICATIONS

UBRELVY is contraindicated:

- In patients with hypersensitivity to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- With concomitant use of strong CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) (see 9.4 Drug-Drug Interactions)**.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The maximum daily dose of UBRELVY should not exceed 200 mg.
- Dose adjustments are recommended in patients with severe hepatic (Child-Pugh Class C) or renal (CrCl 15-29 mL/min) impairment (see 10.3 Pharmacokinetics and 4.2 Recommended Dose and Dosage Adjustment)**.**
- UBRELVY is contraindicated in patients taking strong CYP3A4 inhibitors (see 2 CONTRAINDICATIONS).
- Dose adjustments are recommended in patients who are taking mild or moderate CYP3A4 inhibitors or inducers as well as BCRP and/or P-gp only Inhibitors (see 9.4 Drug-Drug Interactions).
- Consumption of a high-fat meal delays ubrogepant peak plasma concentrations (see 10.3 Pharmacokinetics).

4.2 Recommended Dose and Dosage Adjustment

- **Adults (≥ 18 years of age)**: The recommended dose of UBRELVY is 50 mg or 100 mg taken orally, with or without food. If needed, an optional second dose may be taken, at least 2 hours after the initial dose. The maximum daily dose is 200 mg. The safety of taking more than 16 doses in a 30 day period has not been established.
- **Pediatrics (< 18 years of age)**: Health Canada has not authorized an indication for pediatric use.
- **Geriatrics**: There is limited data available involving the use of UBRELVY in patients aged 65 and over. Caution should be exercised when using UBRELVY in elderly patients. The recommended dose for elderly patients is 50 mg. The optional second dose should also be limited to 50 mg, for a maximum daily dose of 100 mg.
- **Patients with Hepatic Insufficiency**: UBRELVY is metabolized primarily in the liver. Ubrogepant exposure is increased in patients with hepatic impairment. In patients with severe hepatic impairment (Child-Pugh Class C), doses should be limited to 50 mg for both the initial dose and the optional second dose, for a maximum daily dose of 100 mg (see 10.3 Pharmacokinetics).
- **Patients with Renal Insufficiency**: There is limited experience with the use of UBRELVY in patients with renal insufficiency. While renal clearance is not a significant route of elimination for ubrogepant, dose adjustments are recommended for patients with severe renal impairment (CrCl 15-29 mL/min). In these patients, it is recommended that doses be limited to 50 mg for both the initial dose and the optional second dose, for a maximum daily dose of 100 mg. The use of UBRELVY in patients with end-stage renal disease (ESRD) (CrCl <15 mL/min) is not recommended (see 10.3 Pharmacokinetics).

4.3 Reconstitution

Not applicable.

4.4 Administration

UBRELVY should be taken orally, with or without food (see 10.3 Pharmacokinetics).

5 OVERDOSAGE

A supratherapeutic dose of 400 mg (2 times maximum recommended human dose (MRHD)) once daily for 10 days was safe and well tolerated by healthy volunteers. The elimination half-life of ubrogepant is approximately 5 to 7 hours, therefore monitoring of patients after overdose with UBRELVY should continue for at least 24 hours or while symptoms or signs persist.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 50 mg, 100 mg	colloidal silicon dioxide, croscarmellose sodium, mannitol, microcrystalline cellulose, polyvinylpyrrolidone/vinyl acetate copolymer, sodium chloride, sodium stearyl fumarate, vitamin E polyethylene glycol succinate

UBRELVY 50 mg tablets are formulated for oral use as white to off-white, capsule-shaped, biconvex tablets debossed with “U50” on one side.

UBRELVY 100 mg tablets are formulated for oral use as white to off-white, capsule-shaped, biconvex tablets debossed with “U100” on one side.

Tablets are packaged in unit-dose packets and supplied in cartons of:

- 1 packet (physician sample only)
- 10 packets

7 WARNINGS AND PRECAUTIONS

Driving and Operating Machinery

Somnolence is a common adverse event associated with the use of UBRELVY. Patients should be advised to exercise caution when driving or operating a vehicle or potentially dangerous machinery (see 8.2 Clinical Trial Adverse Reactions).

Immune

Hypersensitivity reactions, including rash, urticaria, facial edema, and dyspnea, have been reported with use of UBRELVY. Most reactions occurred within hours after dosing and were not serious. Some hypersensitivity reactions led to discontinuation. If a serious hypersensitivity reaction occurs, discontinue UBRELVY and institute appropriate therapy.

Reproductive Health: Female and Male Potential

The use of UBRELVY may reduce the effectiveness of oral contraceptives. This should be taken into consideration when choosing the dose of oral contraceptives. Supplemental methods of birth control should also be considered (see 9.4 Drug-Drug Interactions).

7.1 Special Populations

7.1.1 Pregnant Women

The use of UBRELVY in pregnant women is not recommended.

The use of UBRELVY in pregnancy during clinical trials was very limited. Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of ubrogepant. UBRELVY should not be used by pregnant women unless the expected benefit to the mother outweighs the potential risk to the fetus.

CGRP may play an important role in supporting a normal healthy pregnancy.

In animal studies, adverse effects on embryofetal development were observed following administration of ubrogepant during pregnancy, including abortion and increased embryofetal mortality in rabbits and decreased body weight in offspring in rats, at doses greater than those used clinically and which were associated with maternal toxicity (see 16 NON-CLINICAL TOXICOLOGY).

In embryofetal toxicity studies in rats and rabbits, there were no treatment-related external visceral, coronal, or skeletal malformations or variations. Therefore, no evidence of teratogenicity has been observed in rats or rabbits with UBRELVY (see 16 NON-CLINICAL TOXICOLOGY)**.**

Several studies have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Pregnancy registry

A registry is being established to collect information about the effect of UBRELVY exposure during pregnancy. Details are forthcoming

7.1.2 Breast-feeding

There are no data on the extent of ubrogepant secretion in human milk, the effects of ubrogepant on the breastfed infant or the effects on milk production. Precaution should be exercised because many drugs can be excreted in human milk.

In lactating rats, oral dosing with ubrogepant resulted in levels of ubrogepant in milk that were comparable to peak plasma concentrations (see 10.3 Pharmacokinetics). Adverse reductions in body weights were observed in pups during the lactation period (see 16 NON-CLINICAL TOXICOLOGY).

The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for UBRELVY and any potential adverse effects on the breastfed infant from UBRELVY or from the underlying maternal condition.

If a mother does use UBRELVY, the breastfed baby should be monitored closely for appropriate weight gain, and developmental milestones.

7.1.3 Pediatrics

Safety and efficacy of UBRELVY in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for use in pediatric patients.

7.1.4 Geriatrics

Clinical studies of UBRELVY did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, elderly patients are more likely to have reduced hepatic and renal function, which may affect ubrogepant exposure. Dose selection for an elderly patient should be cautious, limiting doses to 50 mg for the initial and optional second dose (see 4.2 Recommended Dose and Dosage Adjustment).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Ubrogepant is generally safe and well-tolerated. Most adverse reactions were mild or moderate and the frequencies were low and comparable between ubrogepant and placebo-treated patients. The most commonly reported adverse reactions are nausea, somnolence, and dry mouth (see Table 2).

In an open-label 52 week study 2.5% of patients discontinued due to an adverse event, however, no single event led to discontinuation in more than 2 patients. Incidence of serious adverse events with ubrogepant in this study was low and comparable to usual care, defined as the medications a patient routinely used to relieve a migraine attack (4.1% - usual care; 2.2% ubrogepant 50 mg; 2.9% ubrogepant 100 mg).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of UBRELVY was evaluated in 3664 subjects who received at least one dose of UBRELVY. In the two randomized, double-blind, placebo-controlled, Phase 3 trials in adult patients with migraine (ACHIEVE I and ACHIEVE II), a total of 1439 patients received UBRELVY 50 mg or 100 mg (see 14 CLINICAL TRIALS). Of the UBRELVY-treated patients in these 2 studies, approximately 89% were female, 82% were Caucasian, 15% were Black, 1% were Asian and 17% were of Hispanic or Latino ethnicity. The mean age at study entry was 41 years (range of 18-75).

Adverse reactions in the placebo-controlled studies are shown in Table 2.

Table 2 – Adverse Reactions Occurring with an Incidence of at Least 2% for Either Dose of UBRELVY and at a Frequency at Least Twice the Rate of Placebo in Studies 1 and 2 (ACHIEVE I and II)

	UBRELVY 50 mg n = 954 (%)	UBRELVY 100 mg n = 485 (%)	Placebo n = 984 (%)
Gastrointestinal disorders			
Nausea*	2	4	2
Dry Mouth*	<1	2	1
Psychiatric disorders			
Somnolence*	1	2	1
*The majority of cases were mild and none were serious			

The incidence of adverse reactions in controlled clinical trials was not affected by gender, race, age or cardiovascular risk.

Long-term safety was assessed in 813 patients, dosing intermittently for up to 1 year in an open-label extension study. Patients were permitted to treat up to 8 migraines per month with UBRELVY. A total of 421 patients were exposed to 50 mg or 100 mg of UBRELVY for at least 6 months, and 364 patients were exposed to these doses for at least 1 year, all of whom treated at least 2 migraine attacks per month, on average. In this study 21,454 migraines were treated with UBRELVY. The overall safety profile in the open-label, long-term, 52-week safety study was consistent with the placebo-controlled Studies (ACHIEVE I and II) (see 14 CLINICAL TRIALS).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety and efficacy of UBRELVY have not been studied in pediatric patients.

8.3 Less Common Clinical Trial Adverse Reactions

No less common adverse reactions (<2%), related to UBRELVY, were identified in Clinical Trials.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

No abnormal laboratory findings were identified during clinical trials.

8.5 Post-Market Adverse Reactions

In addition to the adverse reactions reported during clinical studies, the adverse reaction, hypersensitivity (e.g. rash, urticaria, facial edema, dyspnea), has been identified during post-marketing experience.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Ubrogepant is metabolized primarily by cytochrome P450 3A4 (CYP3A4). Drug interactions with medications that are inducers or inhibitors of CYP3A4 have been demonstrated. UBRELVY is contraindicated with concomitant use of strong CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) (see 2 CONTRAINDICATIONS).

Ubrogepant is a weak inhibitor of CYP2C8, 2C9, 2D6, 2C19, MAO-A and UGT1A1. The in vitro inhibition potential is not expected to be clinically significant. Ubrogepant is not an inhibitor of CYP1A2, 2B6, or 3A4. Ubrogepant is not an inducer of CYP1A2, 2B6 or 3A4 at clinically relevant concentrations.

Ubrogepant is a substrate of BCRP and P-gp efflux transporters in vitro; therefore, concomitant use of inhibitors of BCRP and/or P-gp (e.g., quinidine, carvedilol, eltrombopag, curcumin) may increase the exposure of ubrogepant.

Ubrogepant is a weak substrate of OATP1B1, OATP1B3, and OAT1, but not a substrate of OAT3. It is a weak inhibitor of OATP1B1, OATP1B3 and OCT2 transporters. It is not an inhibitor of P-gp, BCRP, BSEP, MRP3, MRP4, OAT1, OAT3, or NTCP transporters.

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been studied.

9.4 Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction studies, or potential drug interactions due to expected magnitude and seriousness of the interaction.

Table 3 – Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Ketoconazole (strong CYP3A4 inhibitor)	CT	10-fold increase in ubrogepant exposure.	UBRELVY is contraindicated for concomitant use with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin) (see 2 CONTRAINDICATIONS).
Verapamil (moderate CYP3A4 inhibitor)	CT	3.5-fold increase in ubrogepant exposure.	Patients concomitantly using moderate CYP3A4 inhibitors (e.g. ciprofloxacin, fluconazole, fluvoxamine, grapefruit juice) should use a single 50 mg dose of UBRELVY and avoid taking a second dose within 24 hours.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Cimetidine (weak CYP3A4 inhibitor)	T	May result in mild increase in ubrogepant exposure.	Patients concomitantly using weak CYP3A4 inhibitors (e.g. cimetidine) should use a 50 mg dose of UBRELVY for the initial dose and optional second dose.
Rifampin (strong CYP3A4 inducer)	CT	80% reduction in ubrogepant exposure.	In patients taking strong CYP3A4 inducers (e.g. phenytoin, rifampin, St. John's Wort) loss of ubrogepant efficacy is expected. The concomitant use of UBRELVY with strong CYP3A4 inducers should be avoided.
Weak or moderate CYP3A4 inducers	T	May reduce ubrogepant exposure.	Co-administration of UBRELVY with weak or moderate CYP3A4 inducers was not evaluated. The 100 mg dose of UBRELVY should be considered when co-administered with weak or moderate CYP3A4 inducers (e.g. armodafinil, modafinil, rufinamide, bosentan, efavirenz, etravirine, phenobarbital, primidone).
Inhibitors of BCRP and/or P-gp efflux transporters (e.g., quinidine, carvedilol, eltrombopag, curcumin)	T	Potential increase of ubrogepant exposure.	Ubrogepant is a substrate of BCRP and P-gp efflux transporters. Clinical drug interaction studies with inhibitors of these transporters have not been conducted. Patients concomitantly taking BCRP and/or P-gp only inhibitors should be advised to use UBRELVY 50 mg for the initial and optional second dose.
Other gepants (e.g. atogepant)	T	Potential for additive pharmacodynamic effects.	Co-administration of UBRELVY with other gepants (e.g. atogepant) has not been investigated. Concomitant administration of UBRELVY with other gepants is not recommended.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Oral Contraceptives	CT	26% reduction in peak plasma concentrations of ethinyl estradiol, no effect on AUC. No effect on norelgestromin PK.	Though not expected to be clinically significant, these reduced plasma levels should be taken into consideration when selecting oral contraceptive doses.
Legend: CT = Clinical Trial; T = Theoretical			

No clinically significant pharmacokinetic interactions were observed when UBRELVY was co-administered with acetaminophen, naproxen, sumatriptan, proton pump inhibitors (e.g., esomeprazole), erenumab or galcanezumab.

9.5 Drug-Food Interactions

UBRELVY may be taken with or without food. When UBRELVY is taken with a high-fat meal, peak plasma concentrations are delayed (see 10.3 Pharmacokinetics)**.** The effect of this delay on the efficacy of UBRELVY remains unknown.

Consumption of grapefruit and grapefruit juice may increase exposure of ubrogepant and should be avoided.

9.6 Drug-Herb Interactions

Interactions of UBRELVY with herbal products have not been studied.

St-John's Wort (*Hypericum perforatum)* is a strong inducer of CYP3A4 and has the potential to significantly reduce ubrogepant exposure. Concomitant use of UBRELVY with St-John's Wort should be avoided.

Curcumin is an inhibitor of P-gp efflux transporters and CYP3A4 enzymes and has the potential to increase ubrogepant exposure. Patients taking curcumin should be advised to limit dosing to UBRELVY 50 mg for the initial dose and optional second dose.

Green tea extracts are inhibitors of intestinal P-gp and CYP3A4 enzymes. The ingestion of green tea extract or its associated catechins is not expected to result in clinically significant influences on ubrogepant exposure. However, some caution is advised in the consumption of significant amounts of green tea beverages or green tea extract in patients prescribed UBRELVY.

9.7 Drug-Laboratory Test Interactions

Interference of UBRELVY with laboratory and/or diagnostic tests has not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Calcitonin gene-related peptide (CGRP) is a neuropeptide present in the peripheral and central nervous system. CGRP is released from sensory nerve endings during a migraine attack, particularly the nerve endings of sensory trigeminal ganglion neurons. Ubrogepant is a small molecule, high affinity (K_i = 0.07nM) CGRP receptor antagonist (gepant) that blocks the binding of CGRP to its receptor and antagonizes CGRP receptor function.

Ubrogepant may relieve migraine by blocking CGRP-induced neurogenic vasodilation, halting the cascade of CGRP-induced neurogenic inflammation, and/or inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus.

In vitro studies in coronary, meningeal and cerebral artery strips indicate that ubrogepant lacks vasoconstrictive effects in cranial and coronary arteries.

10.2 Pharmacodynamics

For pain freedom, pain relief, sustained pain relief, and sustained pain freedom, ubrogepant demonstrates a significant exposure-response relationship. Differences between the 50 mg and 100 mg doses were minimal (see 14 CLINICAL TRIALS).

Abuse liability has not been studied in humans. Animal studies showed no indications of significant abuse potential, drug dependence or withdrawal.

In a double-blind, randomized, placebo- and positive-controlled, 4-period crossover ECG assessment study in healthy subjects (N=72), ubrogepant at single doses of 100 mg (therapeutic) and 400 mg (supratherapeutic) was not observed to have any pharmacodynamic effect on the QTcF interval.

10.3 Pharmacokinetics

Table 4 – Summary of Mean (±SD) Ubrogepant Pharmacokinetic Parameters in Migraine Patients and Healthy Subjects

		C_{max} (ng/mL)	**Median T_{max} (hr)**	**AUC_{0-t} (ng•hr/mL)**
Migraine Patients, Single Dose	Ubrelvy 50 mg	143 (148)	1.01	333 (185)
	Ubrelvy 100 mg	263 (168)	1.95	663 (449)
Healthy Subjects, Single Dose	Ubrelvy 100 mg	274 (99)	1.67	1221 (430)

Absorption

Ubrogepant is rapidly absorbed following oral administration of UBRELVY, with peak plasma concentrations observed around 1.5 hours post-dose.

Ubrogepant displays dose-proportional pharmacokinetics within the range 40 to 400 mg.

When UBRELVY was administered with a high-fat meal, the time to maximum ubrogepant plasma concentration was delayed by 2 hours and resulted in a 20% reduction in C_{max} with no change in AUC. The impact on UBRELVY efficacy of delayed exposure, associated with consumption of a high-fat meal, is unknown. UBRELVY may be taken with or without food.

Distribution

Plasma protein binding of ubrogepant is 87% in vitro. The mean apparent central volume of distribution of ubrogepant (V/F) after single dose oral administration is approximately 350 L.

Metabolism

Ubrogepant is eliminated mainly through metabolism, primarily by CYP3A4. The parent compound (ubrogepant), and 2 glucuronide conjugate metabolites (M15 and M20) were the most prevalent circulating components in human plasma. The glucuronide metabolites are not expected to contribute to the pharmacological activity of ubrogepant, as M15 was approximately 6000-fold less potent in a CGRP receptor binding assay, while M20 is present at extremely low levels.

Elimination

The elimination half-life of ubrogepant is approximately 5-7 hours. The mean apparent oral clearance (CL/F) of ubrogepant is approximately 87 L/hr. Ubrogepant is excreted mostly via the biliary/fecal route, while the renal route is a minor route of elimination. Following single oral dose administration of [^{14}C]-ubrogepant to healthy male subjects, 42% and 6% of the dose was recovered as unchanged ubrogepant in feces and urine, respectively.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of ubrogepant in pediatric patients has not been studied. Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** Assessment of UBRELVY pharmacokinetics in patients 65 years of age and older is limited. The greater frequency of decreased hepatic, renal, or cardiac function, characteristic of the elderly, as well as concomitant disease and use of other medications may impact the pharmacokinetics of UBRELVY in this population. Caution should be exercised when dosing in the elderly (see 4.2 Recommended Dose and Dosage Adjustment).
- **Pregnancy and Breast-feeding:** It is not known whether ubrogepant crosses the placenta in humans or is present in human milk. In lactating rats, oral dosing with ubrogepant resulted in levels of ubrogepant in milk that were comparable to peak plasma levels.

- **Sex:** Based on population PK analysis, no clinically significant differences in the pharmacokinetics of ubrogepant were noted between men and women.
- **Ethnic Origin:** As assessed by population PK analysis, no clinically significant differences in the pharmacokinetics of ubrogepant based on ethnic origin were observed.
- **Hepatic Insufficiency:** In patients with pre-existing mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe hepatic impairment (Child-Pugh Class C), ubrogepant exposure was increased by 7%, 50% and 115%, respectively. No dose adjustment is required for patients that have mild or moderate hepatic impairment. Patients with severe hepatic impairment should be advised to use UBRELVY 50 mg (see 4.2 Recommended Dose and Dosage Adjustment).
- **Renal Insufficiency:** Population pharmacokinetic analysis based on pooled data from clinical studies was used to evaluate the effect of renal impairment characterized based on estimated creatine clearance (CLcr) using the Cockcroft-Gault (C-G) equation. No significant difference in the pharmacokinetics of ubrogepant was predicted in patients with mild to moderate renal impairment (CLcr 30-89 mL/min) relative to those with normal renal function (CLcr >90 mL/min). Patients with severe renal impairment or ESRD (eGFR < 30 mL/min) have not been studied (see 4.2 Recommended Dose and Dosage Adjustment).

11 STORAGE, STABILITY AND DISPOSAL

Store between 15˚C and 30˚C.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

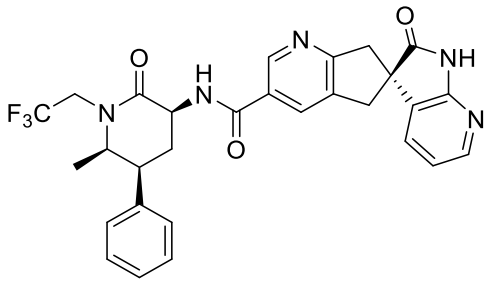
Drug Substance

Proper / Common name: ubrogepant

Chemical name: (3'S)-N-((3S,5S,6R)-6-methyl-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-yl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine-3-carboxamide

Molecular formula and molecular mass: Molecular formula is $C_{29}H_{26}F_3N_5O_3$
Molecular weight is 549.6

Structural formula:



Physicochemical properties: Ubrogepant (as ubrogepant trihydrate) is a white to off-white powder. It is freely soluble in ethanol, methanol, acetone, acetonitrile and practically insoluble in water.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Acute Treatment of Migraine, With or Without Aura

Table 5 – Summary of patient demographics for clinical trials in patients with a history of migraine (modified ITT Population)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (Female %)
UBR-MD-01 (Study 1) ACHIEVE I	Randomized, Double-blind, placebo-controlled, single-attack, efficacy/safety	Placebo Ubrogepant 50 mg Ubrogepant 100 mg Route of Administration: Oral Duration: 60 days	456 423 448	40.8 (18-74) 39.7 (18-70) 40.3 (18-75)	89.3 89.9 86.2
UBR-MD-02 (Study 2) ACHIEVE II	Randomized, Double-blind, placebo-controlled, single-attack, efficacy/safety	Placebo Ubrogepant 50 mg Route of Administration: Oral Duration: 60 days	456 464	41.4 (18-73) 41.1 (18-75)	88.2 91.2

The efficacy of UBRELVY for the acute treatment of migraine was demonstrated in two multicenter, randomized, double-blind, placebo-controlled, single migraine attack studies. These studies enrolled patients with a history of migraine with and without aura, according to the ICHD-3 beta diagnostic criteria, and who experienced 2 to 8 migraine attacks per month with moderate to severe headache pain. In Study 1 (ACHIEVE I), patients were randomized to receive UBRELVY 50 mg or 100 mg or placebo; and in Study 2 (ACHIEVE II), patients were randomized to receive UBRELVY 50 mg or placebo. Patients were permitted to use standard migraine preventive medications during the study. At baseline, 23% percent of patients were taking preventive medications for migraine. The most commonly used preventive medications were topiramate, onabotulinumtoxinA, propranolol, and amitriptyline.

These studies included patients with moderate to high risk for cardiovascular disease (11%) and excluded patients with any clinically significant cardiovascular or cerebrovascular disease.

In all studies, patients were instructed to treat a migraine with moderate to severe headache pain intensity within the first 4 hours of pain onset. An optional second dose of study medication (UBRELVY or placebo) or the patient's usual acute treatment for migraine was

allowed 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache.

The co-primary endpoints were the percentage of patients with:

- Migraine headache pain-freedom, defined as reduction in headache severity from moderate or severe pain to no pain, assessed at 2 hours after initial dosing.
- Most bothersome symptom (MBS) freedom, defined as the absence of the self-identified MBS, other than headache pain (i.e., photophobia, phonophobia, or nausea), assessed at 2 hours after initial dosing.

Among patients who selected a MBS, the most commonly selected was photophobia (56%), followed by phonophobia (24%), and nausea (19%).

Migraine headache pain relief (defined as reduction in headache severity from moderate or severe pain to mild or no pain) and absence of individual symptoms of photophobia, phonophobia, and nausea were assessed at 2 hours after initial dosing, as secondary endpoints.

Sustained pain relief (defined as mild to no pain at 2 hours and continued pain relief without the use of study medication or other acute treatment) and sustained pain freedom (defined as no pain at 2 hours and continued pain freedom without the use of study medication or other acute treatment) were assessed at 24 and 48 hours after dosing.

In both studies, the percentage of patients achieving migraine headache pain freedom and MBS freedom at 2 hours after initial dosing was significantly greater among patients receiving UBRELVY compared to those who received placebo. The results for primary and secondary endpoints are shown in Table 6.

Table 6 – Efficacy Endpoints for ACHIEVE I and ACHIEVE II (modified ITT population[a])

	Study 1			Study 2	
	UBRELVY 50 mg (N[a]=423)	**UBRELVY 100 mg (N[a]=448)**	**Placebo (N[a]=456)**	**UBRELVY 50 mg (N[a]=464)**	**Placebo (N[a]=456)**
Pain Freedom at 2 hours					
N[b]	422	448	456	464	456
% Responders	19.2	21.2	11.8	21.8	14.3
p-value	0.0017	0.0001		0.0065	
Most Bothersome Symptom Free at 2 hours					
N[b]	420	448	454	463	456
% Responders	38.6	37.7	27.8	38.9	27.4
p-value	0.0003	0.0008		0.0005	
Pain Relief at 2 hours					
N[b]	422	448	456	464	456
% Responders	60.7	61.4	49.1	62.7	48.2
p-value	0.0002	0.0002		<0.0001	
Sustained Pain Relief 2-24 hours[d]					
N[c]	413	434	447	449	443
% Responders	36.3	38.0	20.8	36.7	21.0
p-value	<0.0001	<0.0001		<0.0001	
Sustained Pain Freedom 2-24 hours[d]					
N[c]	418	441	452	457	451
% Responders	12.7	15.4	8.6	14.4	8.2
p-value	NS	0.0018		0.0051	

NS: not statistically significant

[a] mITT population: all randomized patients who received at least 1 dose of investigational product, recorded a baseline migraine headache severity measurement, and had ≥ 1 postdose migraine headache severity or migraine-associated symptom measurement at or before the 2-hour timepoint

[b]Number of patients with non-missing endpoints assessment at or before 2 hours after initial dose in the modified intent-to-treat population.

[c]Number of patients with determinable sustained pain relief or sustained pain freedom from 2 to 24 hours after initial dose in the modified intent-to-treat population.

[d]Sustained Pain Freedom and Sustained Pain Relief were also evaluated at 2-48 hours and the results were consistent with the 2-24 hour endpoints.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: At high doses in rats, a decrease in body weight gain and a reversible epithelial vacuolation of the small intestine was observed at exposures 8.5-fold the anticipated clinical exposure (AUC) after a 200 mg dose. No adverse effects were observed in monkeys up to the highest dose level tested which represents an 81-fold margin above the anticipated clinical exposure after a 200 mg dose.

Genotoxicity: Ubrogepant was negative in the Ames test, chromosomal aberration test in Chinese Hamster Ovary cells, and in the in vivo rat bone marrow micronucleus test.

Carcinogenicity: Two-year carcinogenicity studies have been conducted with ubrogepant in CD-1 mice at doses up to 50 mg/kg/day and in Wistar-Han rats at doses up to 100 mg/kg/day in males and 150 mg/kg/day in females. Oral administration of ubrogepant for 104 weeks did not produce tumors in rats or mice. The highest dose tested in mice is similar to the maximum recommended human dose (200 mg/day) on a body surface area (mg/m2) basis. Plasma exposure (AUC) at the highest dose tested in rats is approximately 25 times that in humans at the MRHD of 200 mg/day.

Reproductive and Developmental Toxicology: Oral administration of ubrogepant (1.5, 5, 25, 125 mg/kg/day) to pregnant rats during the period of organogenesis resulted in no embryo-fetal toxicity. Plasma exposure (AUC) at high dose in animals is approximately 45 times that in humans at the MRHD of 200 mg/day.

In a similar study in rabbits at oral doses of 15, 45, 75, or 250 mg/kg/day, maternal toxicity consisting of blood in the cage pan, abortions, body weight loss and decreased food consumption was observed at 250 mg/kg/day and led to early termination of the dose group prior to litter assessment. Maternal toxicity was observed at 75 mg/kg/day however there was no embryo-fetal toxicity at this dose level. Plasma exposure (AUC) at the highest no-effect dose (75 mg/kg/day) for adverse effects on embryofetal development in rabbit is approximately 8 times that in humans at the MRHD.

In the embryo-fetal toxicity studies in rats and rabbits, there were no treatment-related external, visceral, coronal, or skeletal malformations or variations. Ubrogepant was not teratogenic in these studies.

In a prenatal-postnatal development study where rats received oral administration of ubrogepant at doses of 25, 60 and 160 mg/kg/day throughout gestation and lactation, reduced maternal body weights and food consumption at doses ≥ 60 mg/kg/day resulted in reduced body weights in the pups at the same doses. There were no developmental effects on sexual maturation, memory and learning, or fertility. Ubrogepant was excreted into breast milk, with concentrations that were comparable to peak plasma concentrations. Plasma exposure (AUC) at the no-effect dose (25 mg/kg/day) is approximately 15 times that in humans at the MRHD.

Impairment of Fertility: Ubrogepant, at oral doses up to 160 mg/kg/day, was found to have no adverse effect on fertility and reproductive performance of male and female rats.

Juvenile Toxicity: Administration of ubrogepant, at oral doses up to 160 mg/kg/day, to juvenile rats from postnatal day 28 through postnatal day 70 was associated with reductions in body weights and body weight gains and effects on acoustic startle habituation in males at 160 mg/kg/day and learning and memory in the females at ≥ 20 mg/kg/day during the dose period, however, these showed full recovery during the off-dose period and were not considered adverse. There were no other drug related effects observed. The no-observed-adverse-effect level (NOAEL) for the males and females was 160 mg/kg/day. Plasma exposures (AUC) at the NOAEL are approximately 90 times the estimated pediatric exposures.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrUBRELVY®

Ubrogepant tablets

Read this carefully before you start taking **UBRELVY** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **UBRELVY**.

What is UBRELVY used for?

UBRELVY is used to treat migraine attacks with or without aura, in adults.

How does UBRELVY work?

The active ingredient in UBRELVY is ubrogepant, which belongs to a group of medications called *gepants*. UBRELVY works by blocking the activity of a chemical called calcitonin gene-related peptide (CGRP). During a migraine attack, CGRP is released by nerve endings and binds to pain receptors in the brain. UBRELVY prevents CGRP from binding to these pain receptors to alleviate or stop migraine symptoms. UBRELVY does not affect blood vessels.

What are the ingredients in UBRELVY?

Medicinal ingredients: ubrogepant.

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, mannitol, microcrystalline cellulose, polyvinylpyrrolidone vinyl acetate copolymer, sodium chloride, sodium stearyl fumarate, vitamin E polyethylene glycol succinate.

UBRELVY comes in the following dosage forms:

Oral tablet, 50 mg and 100 mg.

Do not use UBRELVY if:

- you have ever had an allergic reaction to UBRELVY or any of the ingredients in UBRELVY
- you are taking medicines known as strong CYP3A4 Inhibitors, such as ketoconazole, itraconazole, clarithromycin.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take UBRELVY. Talk about any health conditions or problems you may have, including if you:

- have a serious liver disease.
- have serious kidney disease.

Other warnings you should know about:

Driving and using machines

While using UBRELVY you may feel sleepy. Before driving a vehicle or using machinery, wait to see how you feel after taking UBRELVY.

Children and adolescents

Do not give UBRELVY to children under 18 years of age since the use of UBRELVY has not been studied in children under 18 years of age.

Oral Contraceptives

Your healthcare provider can help you choose the right oral contraceptive to use with UBRELVY. Additional methods of birth control can be used to supplement oral contraceptives.

Pregnancy and Breast-feeding

UBRELVY has not been studied in pregnant women. It is not known if UBRELVY will harm your unborn baby. Talk to your healthcare professional if you are trying to get pregnant or think you may be pregnant when taking UBRELVY. Your healthcare professional will discuss with you the potential risks of taking UBRELVY during pregnancy.

A pregnancy registry for women taking UBRELVY during pregnancy will be available soon. This registry will collect information about your health and your baby's health. If you become pregnant while taking UBRELVY, talk with your doctor about taking part in this registry.

It is not known if UBRELVY passes through breast milk. It is important to tell your healthcare professional if you are breastfeeding or plan to breastfeed. Your healthcare professional will then help you decide if you should stop breast-feeding or stop taking UBRELVY. If you breastfeed while taking UBRELVY, your healthcare professional may tell you to monitor your baby's weight and developmental milestones.

Elderly

If you are over 65 years of age, your healthcare professional may tell you to use the lowest dose of UBRELVY. Check with your healthcare professional, if you are not sure.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with UBRELVY:

- Medicines for fungal infections such as ketoconazole, itraconazole, and fluconazole.
- Antibiotics such as clarithromycin, ciprofloxacin, and rifampin.
- Medicines for high blood pressure such as verapamil, carvedilol, and bosentan.
- Medicines for seizures such as phenytoin, rufinamide, and primidone.
- Medicines known as barbiturates.
- Fluvoxamine, a medicine for depression / obsessive-compulsive disorder.
- Cimetidine, a medicine for heart burn and ulcers.
- Medicines for sleep disorders such as armodafinil and modafinil
- HIV medicines as such efavirenz and etravirine
- Quinidine, a medicine for heart disorders.
- Eltrombopag, medicine for blood disorders.
- Other medicines known as “gepants”.
- Oral contraceptives.
- Grapefruit and grapefruit juice.
- St. John’s Wort.
- Curcumin (turmeric).
- Large amounts of green tea beverages or green tea extract.

How to take UBRELVY:

- Always use UBRELVY exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.

Usual dose:

- The recommended dose of UBRELVY is 50 mg or 100 mg taken orally with or without food.
- If needed, an optional second dose may be taken at least 2 hours after the initial dose.
- The maximum daily dose is 200 mg.
- It is not known if it is safe to take more than 16 doses in a 30-day period.
- Do not exceed the recommended dose prescribed by your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much UBRELVY, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using UBRELVY?

These are not all the possible side effects you may feel when taking UBRELVY. If you experience any side effects not listed here, contact your healthcare professional.

Possible side effects include the following listed below. Most of these side effects are mild to moderate. If these side effects become severe, please tell your healthcare professional.

- Nausea
- Dry Mouth
- Sleepiness

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Hypersensitivity (allergic reaction): rash, hives, facial swelling, and/or shortness of breath.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store this medication between 15°C and 30°C.

Do not use this medicine after the expiry date, which is stated on the carton.

Keep out of reach and sight of children.

If you want more information about UBRELVY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.abbvie.ca or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

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