QULIPTA 10 mg
QULIPTA 30 mg
QULIPTA 60 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

QULIPTA 10 mg
Each tablet contains 10 mg of atogepant (equivalent to 10.3 mg of atogepant free base monohydrate).

QULIPTA 30 mg
Each tablet contains 30 mg of atogepant (equivalent to 30.9 mg of atogepant free base monohydrate).

QULIPTA 60 mg
Each tablet contains 60 mg of atogepant (equivalent to 61.8 mg of atogepant free base monohydrate).

1 INDICATIONS AND USAGE

QULIPTA is indicated for the preventive treatment of migraine in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

QULIPTA is taken orally with or without food.

Episodic Migraine

The recommended dosage of QULIPTA for episodic migraine is 10 mg, 30 mg, or 60 mg taken once daily.

Chronic Migraine

The recommended dosage of QULIPTA for chronic migraine is 60 mg taken once daily.

2.2 Dosage Modifications

Dosing modifications for concomitant use of specific drugs and for patients with renal impairment are provided in Table 1.

Table 1: Dosage Modifications for Drug Interactions and for Specific Populations

Dosage Modifications	Recommended Once Daily Dosage for Episodic Migraine	Usage and Recommended Once Daily Dosage for Chronic Migraine
Concomitant Drug *[see Drug Interactions (7)]*		
Strong CYP3A4 Inhibitors *(7.1)*	10 mg	Avoid use
Strong, Moderate or Weak CYP3A4 Inducers *(7.2)*	30 mg or 60 mg	Avoid use
OATP Inhibitors *(7.3)*	10 mg or 30 mg	30 mg
Renal Impairment *[see Use in Specific Populations (8)]*		
Severe Renal Impairment and End-Stage Renal Disease (CLcr <30 mL/min) *(8.6)*	10 mg	Avoid use

3 DOSAGE FORMS AND STRENGTHS

QULIPTA 10 mg is supplied as white to off-white, round biconvex tablets debossed with “A” and “10” on one side.

QULIPTA 30 mg is supplied as white to off-white, oval biconvex tablets debossed with “A30” on one side.

QULIPTA 60 mg is supplied as white to off-white, oval biconvex tablets debossed with “A60” on one side.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.
Hypersensitivity reactions have included anaphylaxis and dyspnea *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, dyspnea, rash, pruritus, urticaria, and facial edema, have been reported with use of QULIPTA *[see Adverse Reactions (6.2)]*. Hypersensitivity reactions can occur days after administration. If a hypersensitivity reaction occurs, discontinue QULIPTA and institute appropriate therapy *[see Contraindications (4)]*.

5.2 Hypertension

Development of hypertension and worsening of pre-existing hypertension have been reported following the use of CGRP antagonists, including QULIPTA, in the postmarketing setting. Some of the patients who developed new-onset hypertension had risk factors for hypertension. There were cases requiring initiation of pharmacological treatment for hypertension and, in some cases, hospitalization. Hypertension may occur at any time during treatment, but was most frequently reported within 7 days of therapy initiation. QULIPTA was discontinued in many of the reported cases.

Monitor patients treated with QULIPTA for new-onset hypertension, or worsening of pre-existing hypertension, and consider whether discontinuation of QULIPTA is warranted if evaluation fails to establish an alternative etiology or blood pressure is inadequately controlled.

5.3 Raynaud’s Phenomenon

Development of Raynaud’s phenomenon and recurrence or worsening of pre-existing Raynaud’s phenomenon have been reported in the postmarketing setting following the use of CGRP antagonists, including QULIPTA. In reported cases with small molecule CGRP antagonists, symptom onset occurred a median of 1.5 days following dosing. Many of the cases reported serious outcomes, including hospitalizations and disability, generally related to debilitating pain. In most reported cases, discontinuation of the CGRP antagonist resulted in resolution of symptoms.

QULIPTA should be discontinued if signs or symptoms of Raynaud’s phenomenon develop, and patients should be evaluated by a healthcare provider if symptoms do not resolve. Patients with a history of Raynaud’s phenomenon should be monitored for, and informed about the possibility of, worsening or recurrence of signs and symptoms.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*
- Raynaud's Phenomenon *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of QULIPTA was evaluated in 2657 patients with migraine who received at least one dose of QULIPTA. Of these, 1225 patients were exposed to QULIPTA for at least 6 months, and 826 patients were exposed for 12 months.

In the 12-week, placebo-controlled clinical studies (Studies 1,2, and 3), 314 patients received at least one dose of QULIPTA 10 mg once daily, 411 patients received at least one dose of QULIPTA 30 mg once daily, 678 patients received at least one dose of QULIPTA 60 mg once daily, and 663 patients received placebo *[see Clinical Studies (14)]*. Approximately 88% were female, 75% were White, 13% were Black, 10% were Asian, and 10% were of Hispanic or Latino ethnicity. The mean age at study entry was 41 years (range 18 to 74 years).

The most common adverse reactions (incidence at least 4% and greater than placebo) are nausea, constipation, and fatigue/somnolence.

Table 2 summarizes the adverse reactions that occurred during Studies 1,2, and 3.

Table 2: Adverse Reactions Occurring with an Incidence of At Least 2% for QULIPTA and Greater than Placebo in Studies 1, 2 and 3*

	Placebo (N= 663) %	**QULIPTA 10 mg (N=314) %**	**QULIPTA 30 mg (N=411) %**	**QULIPTA 60 mg (N=678) %**
Nausea	3	5	6	9
Constipation	2	6	6	8
Fatigue/Somnolence	4	4	4	5
Decreased Appetite	<1	2	1	3
Dizziness	2	2	2	3

* 10 mg and 30 mg incidence from Studies 1 and 2; 60 mg pooled incidence from Studies 1, 2, and 3.

The adverse reactions that most commonly led to discontinuation of QULIPTA in these studies were nausea (0.6%), constipation (0.5%), and fatigue/somnolence (0.2%).

Liver Enzyme Elevations

In Study 1, Study 2, and Study 3, the rate of transaminase elevations over 3 times the upper limit of normal was similar between patients treated with QULIPTA (0.9%) and those treated with placebo (1.2%). However, there were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with QULIPTA treatment; these were asymptomatic and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice.

Decreases in Body Weight

In Study 1, Study 2, and Study 3, the proportion of patients with a weight decrease of at least 7% at any point was 2.5% for placebo, 3.8% for QULIPTA 10 mg, 3.2% for QULIPTA 30 mg, and 5.3% for QULIPTA 60 mg.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of QULIPTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity (e.g., anaphylaxis, dyspnea, rash, pruritus, urticaria, facial edema) *[see Contraindications (4) and Warnings and Precautions (5.1)]*

Vascular Disorders: Hypertension *[see Warnings and Precautions (5.2)]*, Raynaud's phenomenon *[see Warnings and Precautions (5.3)]*

Effects on ability to drive and use machines

QULIPTA has no or negligible influence on the ability to drive and use machines.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

Coadministration of QULIPTA with itraconazole, a strong CYP3A4 inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects *[see Clinical Pharmacology (12.3)]*. For episodic migraine, the recommended dosage of QULIPTA with concomitant use of strong CYP3A4 inhibitors is 10 mg once daily. For chronic migraine, avoid concomitant use of strong CYP3A4 inhibitors with QULIPTA *[see Dosage and Administration (2.2)]*. No dosage adjustment of QULIPTA is needed with concomitant use of moderate or weak CYP3A4 inhibitors.

7.2 CYP3A4 Inducers

Coadministration of QULIPTA with steady state rifampin, a strong CYP3A4 inducer, resulted in a significant decrease in exposure of atogepant in healthy subjects *[see Clinical Pharmacology (12.3)]*. Concomitant administration of QULIPTA with moderate inducers of CYP3A4 can also result in decreased exposure of atogepant. Coadministration of QULIPTA with steady-state topiramate, a weak CYP3A4 inducer, resulted in decreased exposure of atogepant in healthy subjects *[see Clinical Pharmacology (12.3)]*.

For episodic migraine, the recommended dosage of QULIPTA with concomitant use of strong, moderate, or weak CYP3A4 inducers is 30 mg or 60 mg once daily *[see Dosage and Administration (2.2)]*.

For chronic migraine, avoid concomitant use of strong, moderate, or weak CYP3A4 inducers with QULIPTA *[see Dosage and Administration (2.2)]*.

7.3 OATP Inhibitors

Coadministration of QULIPTA with single dose rifampin, an OATP inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects *[see Clinical Pharmacology (12.3)]*. For episodic migraine, the recommended dosage of QULIPTA with concomitant use of OATP inhibitors is 10 mg or 30 mg once daily. For chronic migraine, the recommended dosage of QULIPTA with concomitant use of OATP inhibitors is 30 mg once daily *[see Dosage and Administration (2.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of QULIPTA in pregnant women. In animal studies, oral administration of atogepant during the period of organogenesis (rats and rabbits) or throughout pregnancy and lactation (rats) resulted in adverse developmental effects (decreased fetal and offspring body weight in rats; increased incidence of fetal structural variations in rabbits) at exposures greater than those used clinically *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The estimated rate of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Data

Animal Data

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreases in fetal body weight and in skeletal ossification at the two highest doses tested (125 and 750 mg/kg), which were not associated with maternal toxicity. At the no-effect dose (15 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 4 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Oral administration of atogepant (0, 30, 90, or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in an increase in fetal visceral and skeletal variations at the highest dose tested (130 mg/kg/day), which was associated with minimal maternal toxicity. At the no-effect dose (90 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 3 times that in humans at the MRHD.

Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in decreased pup body weight at the highest dose tested (125 mg/kg/day), which persisted into adulthood. At the no-effect dose (45 mg/kg/day) for adverse effects on pre- and postnatal development, plasma exposure (AUC) was approximately 5 times that in humans at the MRHD.

8.2 Lactation

Risk Summary

Data from a lactation study in twelve healthy adult females indicate that atogepant is excreted in breast milk in low amounts. The estimated relative infant dose is approximately 0.19% of the maternal weight-adjusted dose, and the milk-to-plasma ratio is 0.08 *(see Data).* There are no data on the effects of atogepant on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for QULIPTA and any potential adverse effects on the breastfed infant from QULIPTA or from the underlying maternal condition.

Data

A study was conducted in twelve healthy adult lactating females who were between 23 and 34 years of age and between 1 month and 6 months postpartum. Each subject was administered a single oral dose of atogepant 60 mg. Maternal plasma and breast milk were collected for 24 hours after dosing. Using a 150 mL/kg/day estimated infant milk intake, the mean estimated relative infant dose was approximately 0.19% of the maternal weight-adjusted dose. The mean milk-to-plasma ratio was 0.08. All subjects had detectable levels of atogepant in breast milk during the study; by 16 to 24 hours after dosing, 25% of females in the study had detectable levels of atogepant in breast milk. The mean cumulative amount of atogepant excreted in breast milk over 24 hours was less than 0.01 mg of a 60 mg dose.

8.4 Pediatric Use

The safety and efficacy in children and adolescents under the age of 18 years have not yet been established.

8.5 Geriatric Use

Population pharmacokinetic modeling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects. Clinical studies of QULIPTA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

The renal route of elimination plays a minor role in the clearance of atogepant *[see Clinical Pharmacology (12.3)]*. For episodic migraine, in patients with severe renal impairment (CLcr 15-29 mL/min) and in patients with end-stage renal disease (ESRD) (CLcr <15 mL/min), the recommended dosage of QULIPTA is 10 mg once daily; in patients with ESRD undergoing intermittent dialysis, QULIPTA should preferably be taken after dialysis *[see Dosage and Administration (2.2)]*. For chronic migraine, avoid use of QULIPTA in patients with severe renal impairment and in patients with ESRD. No dose adjustment is recommended for patients with mild or moderate renal impairment.

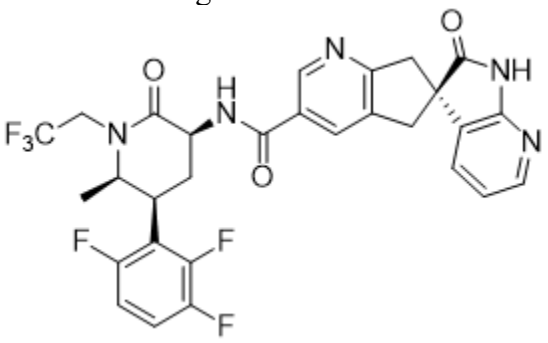
8.7 Hepatic Impairment

No dose adjustment of QULIPTA is recommended for patients with mild or moderate hepatic impairment. Avoid use of QULIPTA in patients with severe hepatic impairment *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

The active ingredient of QULIPTA is atogepant, a calcitonin gene-related peptide (CGRP) receptor antagonist. The chemical name of atogepant is (3'*S*)-*N*-[(3*S*,5*S*,6*R*)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-

trifluorophenyl)piperidin-3-yl]-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide, and it has the following structural formula:



The molecular formula is $C_{29}H_{23}F_6N_5O_3$ and molecular weight is 603.5. Atogepant is a white to off-white powder. It is freely soluble in ethanol, soluble in methanol, sparingly soluble in acetone, slightly soluble in acetonitrile, and practically insoluble in water.

QULIPTA is available as tablets for oral administration containing 10 mg, 30 mg, or 60 mg atogepant. The inactive ingredients include polyvinylpyrrolidone/ vinyl acetate copolymer, mannitol, microcrystalline cellulose, sodium chloride, croscarmellose sodium, vitamin E polyethylene glycol succinate, sodium stearyl fumarate and colloidal silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 5 times the maximum recommended daily dose, QULIPTA does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Following oral administration of QULIPTA, atogepant is absorbed with peak plasma concentrations at approximately 1 to 2 hours. Atogepant displays dose-proportional pharmacokinetics up to 170 mg per day (approximately 3 times the highest recommended dosage), with no accumulation.

Effect of Food

When QULIPTA was administered with a high-fat meal, the food effect was not significant (AUC and C_{max} were reduced by approximately 18% and 22%, respectively, with no effect on median time to maximum atogepant plasma concentration). QULIPTA was administered without regard to food in clinical efficacy studies.

Distribution

Plasma protein binding of atogepant was not concentration-dependent in the range of 0.1 to 10 μM; the unbound fraction of atogepant was approximately 4.7% in human plasma. The mean apparent volume of distribution of atogepant (Vz/F) after oral administration is approximately 292 L.

Elimination

Metabolism

Atogepant is eliminated mainly through metabolism, primarily by CYP3A4. The parent compound (atogepant), and a glucuronide conjugate metabolite (M23) were the most prevalent circulating components in human plasma.

Excretion

The elimination half-life of atogepant is approximately 11 hours. The mean apparent oral clearance (CL/F) of atogepant is approximately 19 L/hr. Following single oral dose of 50 mg ^{14}C-atogepant to healthy male subjects, 42% and 5% of the dose was recovered as unchanged atogepant in feces and urine, respectively.

Specific Populations

Patients with Renal Impairment

The renal route of elimination plays a minor role in the clearance of atogepant. Based on a population pharmacokinetic analysis, there is no significant difference in the pharmacokinetics of atogepant in patients with mild or 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 end-stage renal disease (ESRD; CLcr <30 mL/min) have not been studied *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

In patients with pre-existing mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment, the total atogepant exposure was increased by 24%, 15%, and 38%, respectively. Due to a potential for liver injury in patients with severe hepatic impairment, avoid use of QULIPTA in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

Other Specific Populations

Based on a population pharmacokinetic analysis, age, sex, race, and body weight did not have a significant effect on the pharmacokinetics (C_{max} and AUC) of atogepant. Therefore, no dose adjustments are warranted based on these factors.

Drug Interactions

In Vitro Studies

Enzymes

In vitro, atogepant is not an inhibitor for CYPs 3A4, 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations. Atogepant does not inhibit MAO-A or UGT1A1 at clinically relevant concentrations. Atogepant is not anticipated to be a clinically significant perpetrator of drug-drug interactions through CYP450s, MAO-A, or UGT1A1 inhibition.

Atogepant is not an inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Transporters

Atogepant is a substrate of P-gp, BCRP, OATP1B1, OATP1B3, and OAT1. Dose adjustment for concomitant use of QULIPTA with inhibitors of OATP is recommended based on a clinical interaction study with a OATP inhibitor *[see Dosage and Administration (2.2)]*.

Coadministration of atogepant with BCRP and/or P-gp inhibitors is not expected to increase the exposure of atogepant. Atogepant is not a substrate of OAT3, OCT2, or MATE1.

Atogepant is not an inhibitor of P-gp, BCRP, OAT1, OAT3, NTCP, BSEP, MRP3, or MRP4 at clinically relevant concentrations. Atogepant is a weak inhibitor of OATP1B1, OATP1B3, OCT1, and MATE1. No clinical drug interactions are expected for atogepant as a perpetrator with these transporters.

In Vivo Studies

CYP3A4 Inhibitors

Co-administration of QULIPTA with itraconazole, a strong CYP3A4 inhibitor, resulted in a clinically significant increase (C_{max} by 2.15-fold and AUC by 5.5-fold) in the exposure of atogepant in healthy subjects *[see Drug Interactions (7.1)]*.

Physiologically based pharmacokinetic (PBPK) modeling suggested co-administration of QULIPTA with moderate or weak CYP3A4 inhibitors increase atogepant AUC by 1.7- and 1.1- fold, respectively. The changes in atogepant exposure when coadministered with weak or moderate CYP3A4 inhibitors are not expected to be clinically significant.

CYP3A4 Inducers

Co-administration of QULIPTA with rifampin, a strong CYP3A4 inducer, decreased atogepant AUC by 60% and C_{max} by 30% in healthy subjects *[see Drug Interactions (7.2)]*. No dedicated drug interaction studies were conducted to assess concomitant use with moderate CYP3A4 inducers. Moderate inducers of CYP3A4 can decrease atogepant exposure *[see Drug Interactions (7.2)]*. Co-administration of QULIPTA with topiramate, a weak inducer of CYP3A4, decreased atogepant mean steady-state AUC $_{0-\tau}$ by 25% and mean steady-state C_{max} by 24% in healthy subjects *[see Drug Interactions (7.2)]*.

BCRP/OATP/P-gp Inhibitors

Co-administration of QULIPTA with single dose rifampin, an OATP inhibitor, increased atogepant AUC by 2.85-fold and C_{max} by 2.23-fold in healthy subjects *[see Drug Interactions (7.3)]*.

Co-administration of QULIPTA with quinidine, a P-gp inhibitor, increased atogepant AUC by 26% and C_{max} by 4% in healthy subjects. The changes in atogepant exposure when co-administered with P-gp inhibitors are not expected to be clinically significant.

PBPK modeling suggests that co-administration of QULIPTA with BCRP inhibitors increases atogepant exposure by 1.2-fold. This increase is not expected to be clinically significant.

Other Drug Interaction Evaluations

Co-administration of QULIPTA with oral contraceptive components ethinyl estradiol and levonorgestrel, famotidine, esomeprazole, acetaminophen, naproxen, sumatriptan, or ubrogepant did not result in significant pharmacokinetic interactions for either atogepant or co-administered drugs. Co-administration of QULIPTA with topiramate did not result in clinically significant changes in the pharmacokinetics of topiramate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Atogepant was administered orally to mice (0, 5, 20, or 75 mg/kg/day in males; 0, 5, 30, 160 mg/kg/day in females) and rats (0, 10, 20, or 100 mg/kg in males; 0, 25, 65, or 200 mg/kg in females) for up to 2 years. There was no evidence of drug-related tumors in either species. Plasma exposures at the highest doses tested in mice and rats were approximately 8 and 20-35 times, respectively, that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Mutagenicity

Atogepant was negative in in vitro (Ames, chromosomal aberration test in Chinese Hamster Ovary cells) and in vivo (rat bone marrow micronucleus) assays.

Impairment of Fertility

Oral administration of atogepant (0, 5, 20, or 125 mg/kg/day) to male and female rats prior to and during mating and continuing in females to Gestation Day 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest dose tested are approximately 15 times that in humans at the MRHD.

14 CLINICAL STUDIES

14.1 Episodic Migraine

The efficacy of QULIPTA for the preventive treatment of episodic migraine in adults was demonstrated in two randomized, multicenter, double-blind, placebo-controlled studies (Study 1 and Study 2). The studies enrolled patients with at least a 1-year history of migraine with or without aura, according to the International Classification of Headache Disorders (ICHD-3) diagnostic criteria.

In Study 1 (NCT03777059), 910 patients were randomized 1:1:1:1 to receive QULIPTA 10 mg (N = 222), QULIPTA 30 mg (N = 230), QULIPTA 60 mg (N = 235), or placebo (N = 223), once daily for 12 weeks. In Study 2 (NCT02848326), 652 patients were randomized 1:2:2:2 to receive QULIPTA 10 mg (N = 94), QULIPTA 30 mg (N = 185), QULIPTA 60 mg (N = 187), or placebo (N = 186), once daily for 12 weeks. In both studies, patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, acetaminophen, and opioids) as needed. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine. The studies excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening.

Study 1

The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) across the 12-week treatment period. Secondary endpoints included the change from baseline in mean monthly headache days, the change from baseline in mean monthly acute medication use days, the proportion of patients achieving at least a 50% reduction from baseline in mean MMD (3-month average), the change from baseline in mean monthly Activity Impairment in Migraine-Diary (AIM-D) Performance of Daily Activities (PDA) domain scores, the change from baseline in mean monthly AIM-D Physical Impairment (PI) domain scores, across the 12-week treatment period, and the change from baseline at Week 12 for Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive (RFR) domain scores.

The AIM-D evaluates difficulty with performance of daily activities (PDA domain) and physical impairment (PI domain) due to migraine, with scores ranging from 0 to 100. Higher scores indicate greater impact of migraine, and reductions from baseline indicate improvement. The MSQ v2.1 Role Function-Restrictive (RFR) domain score assesses how often migraine impacts function related to daily social and work-related activities over the past 4 weeks, with scores ranging from 0 to 100. Higher scores indicate lesser impact of migraine on daily activities, and increases from baseline indicate improvement.

Patients had a mean age of 42 years (range 18 to 73 years), 89% were female, 83% were White, 14% were Black, and 9% were of Hispanic or Latino ethnicity. The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. A total of 805 (88%) patients completed the 12-week double-blind study period. Key efficacy results of Study 1 are summarized in Table 3.

Table 3: Efficacy Endpoints in Study 1

	QULIPTA 10 mg N=214	QULIPTA 30 mg N=223	QULIPTA 60 mg N=222	Placebo N=214
Monthly Migraine Days (MMD) across 12 weeks				
Baseline	7.5	7.9	7.8	7.5
Mean change from baseline	-3.7	-3.9	-4.2	-2.5
Difference from placebo	-1.2	-1.4	-1.7	
p-value	<0.001	<0.001	<0.001	
Monthly Headache Days across 12 weeks				
Baseline	8.4	8.8	9.0	8.4
Mean change from baseline	-3.9	-4.0	-4.2	-2.5
Difference from placebo	-1.4	-1.5	-1.7	
p-value	<0.001	<0.001	<0.001	
Monthly Acute Medication Use Days across 12 weeks				
Baseline	6.6	6.7	6.9	6.5
Mean change from baseline	-3.7	-3.7	-3.9	-2.4
Difference from placebo	-1.3	-1.3	-1.5	
p-value	<0.001	<0.001	<0.001	
≥ 50% MMD Responders across 12 weeks				
% Responders	56	59	61	29
Difference from placebo (%)	27	30	32	
p-value	<0.001	<0.001	<0.001	
MSQ v2.1 RFR Domain* at week 12				
Baseline	44.9	44.0	46.8	46.8
Mean change from baseline	30.4	30.5	31.3	20.5
Difference from placebo	9.9	10.1	10.8	
p-value	<0.001	<0.001	<0.001	
AIM-D PDA Domain across 12 weeks**				
Baseline	15.5	16.9	15.9	15.2
Mean change from baseline	-7.3	-8.6	-9.4	-6.1
Difference from placebo	-1.2	-2.5	-3.3	
p-value	NS†	<0.001	<0.001	
AIM-D PI Domain* across 12 weeks**				
Baseline	11.7	13.0	11.6	11.2
Mean change from baseline	-5.1	-6.0	-6.5	-4.0
Difference from placebo	-1.1	-2.0	-2.5	
p-value	NS†	0.002	<0.001	

* Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score
** Activity Impairment in Migraine-Diary Performance of Daily Activities domain score
*** Activity Impairment in Migraine-Diary Physical Impairment domain score
†Not statistically significant (NS)

Figure 1 shows the mean change from baseline in MMD in Study 1. Patients treated with QULIPTA had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo.

Figure 1: Change from Baseline in Monthly Migraine Days in Study 1

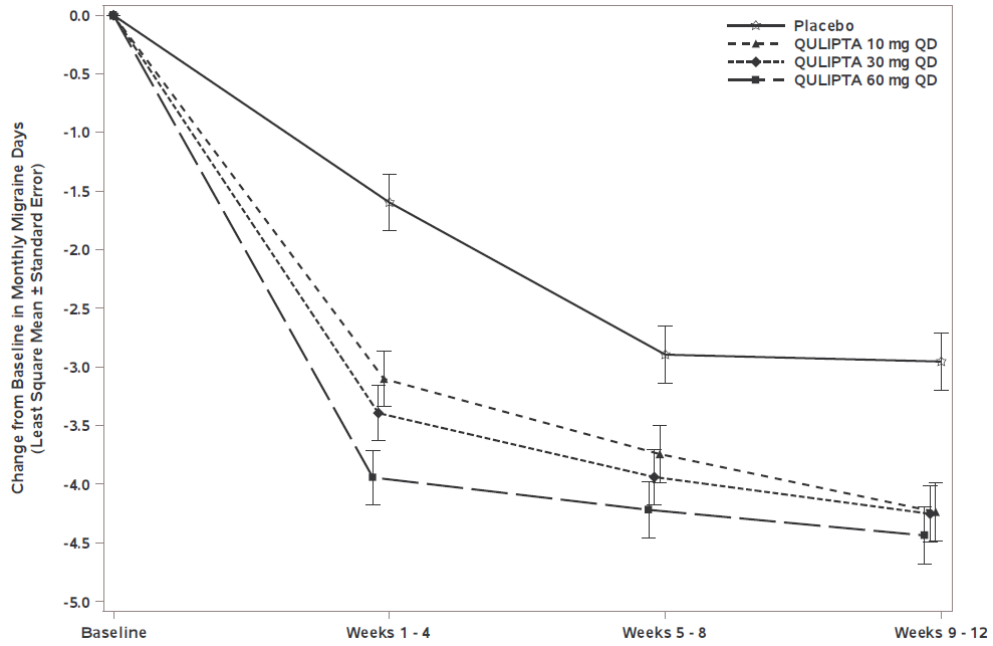
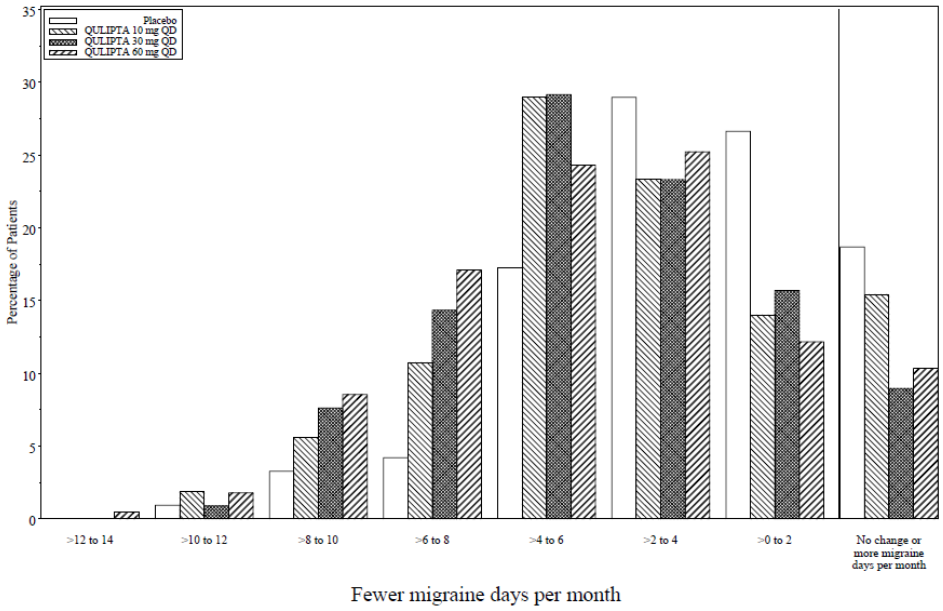


Figure 2 shows the distribution of change from baseline in mean MMD across the 12-week treatment period, in 2-day increments, by treatment group. A treatment benefit over placebo for all doses of QULIPTA is seen across a range of mean changes from baseline in MMD.

Figure 2: Distribution of Change from Baseline in Mean Monthly Migraine Days by Treatment Group in Study 1



Study 2

The primary efficacy endpoint was the change from baseline in mean monthly migraine days across the 12-week treatment period.

Patients had a mean age of 40 years (range: 18 to 74 years), 87% were female, 76% were White, 20% were Black, and 15% were of Hispanic or Latino ethnicity. The mean migraine frequency at baseline was

approximately 8 migraine days per month. A total of 541 (83%) patients completed the 12-week double-blind study period.

In Study 2, there was a significantly greater reduction in mean monthly migraine days across the 12-week treatment period in all three QULIPTA treatment groups, compared with placebo, as summarized in Table 4.

Table 4: Efficacy Endpoints in Study 2

	QULIPTA 10 mg N=92	**QULIPTA 30 mg N=182**	**QULIPTA 60 mg N=177**	**Placebo N=178**
Monthly Migraine Days (MMD) across 12 weeks				
Baseline	7.6	7.6	7.7	7.8
Mean change from baseline	-4.0	-3.8	-3.6	-2.8
Difference from placebo	-1.1	-0.9	-0.7	
p-value	0.024	0.039	0.039	
Monthly Headache Days across 12 weeks				
Baseline	8.9	8.7	8.9	9.1
Mean change from baseline	-4.3	-4.2	-3.9	-2.9
Difference from placebo	-1.4	-1.2	-0.9	
p-value	0.024	0.039	0.039	

Figure 3 shows the mean change from baseline in MMD in Study 2. Patients treated with QULIPTA had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo.

Figure 3: Change from Baseline in Monthly Migraine Days in Study 2

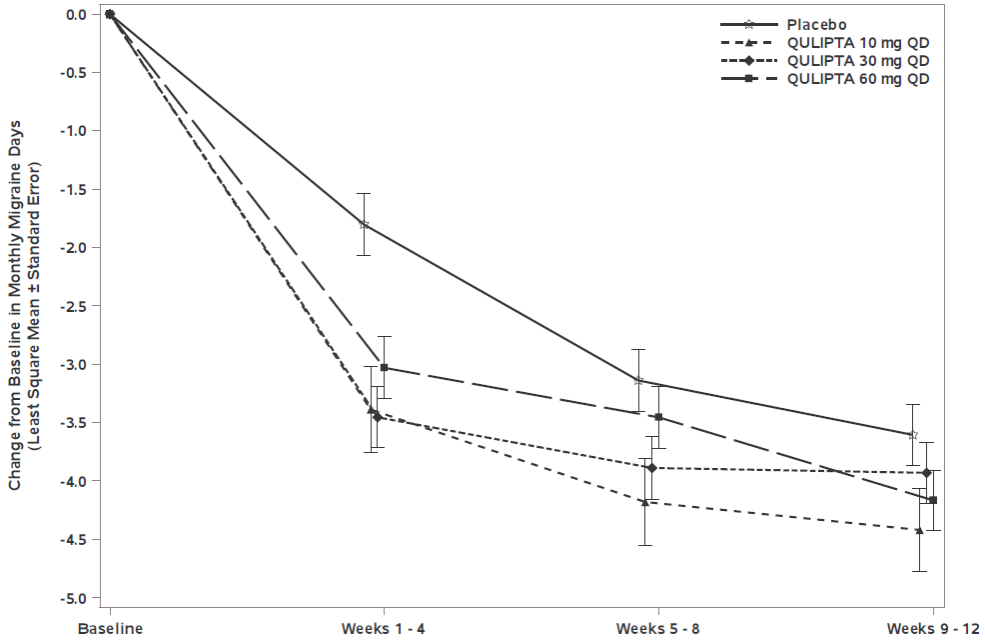
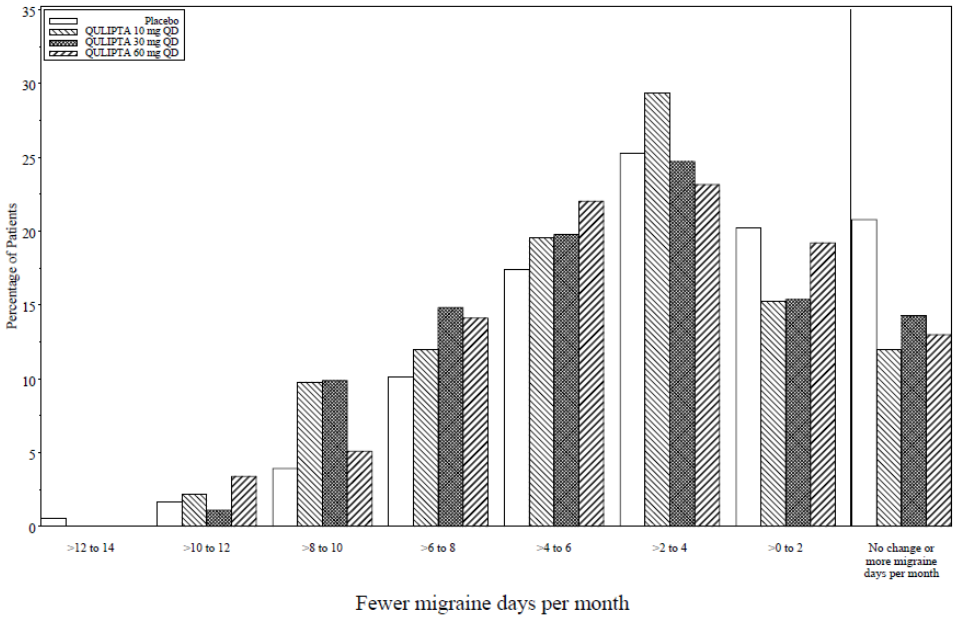


Figure 4 shows the distribution of change from baseline in mean MMD across the 12 week treatment period, in 2-day increments, by treatment group. A treatment benefit over placebo for all doses of QULIPTA is seen across a range of mean changes from baseline in MMD.

Figure 4: Distribution of Change from Baseline in Mean Monthly Migraine Days by Treatment Group in Study 2



14.2 Chronic Migraine

Study 3

The efficacy of QULIPTA for the preventive treatment of chronic migraine in adults was demonstrated in a randomized, multicenter, double-blind, placebo-controlled study (Study 3). The study enrolled patients with at least a 1-year history of chronic migraine, according to the ICHD-3 diagnostic criteria.

Study 3 (NCT03855137) included randomization of patients to QULIPTA 60 mg once daily (N = 262) or placebo (N = 259) for 12 weeks. A subset of patients (11%) was allowed to use one concomitant migraine preventive medication. Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, acetaminophen, and opioids) as needed. Patients with medication overuse headache also were enrolled. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine. The study excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening.

The primary efficacy endpoint was the change from baseline in mean MMD across the 12-week treatment period. Secondary endpoints included the change from baseline in mean monthly headache days, the change from baseline in mean monthly acute medication use days, the proportion of patients achieving at least a 50% reduction from baseline in mean MMD (3-month average), the change from baseline in mean monthly AIM-D PDA domain scores, the change from baseline in mean monthly AIM-D PI domain scores, across the 12-week treatment period, and the change from baseline at Week 12 for MSQ v2.1 RFR domain scores.

Patients had a mean age of 42 years (range 18 to 74 years), 87% were female, 60% were White, 3% were Black, 36% were Asian, and 4% were of Hispanic or Latino ethnicity. The mean migraine frequency at baseline was approximately 19 migraine days per month and was similar across treatment groups. A total of 463 (89%) of these patients completed the 12-week double-blind study period.

Key efficacy results of Study 3 are summarized in Table 5.

Table 4: Efficacy Endpoints in Study 3

	QULIPTA 60 mg QD N=256	**Placebo N=246**
Monthly Migraine Days (MMD) across 12 weeks		

Baseline	19.2	18.9
Mean change from baseline	-6.9	-5.1
Difference from placebo	-1.8	
p-value	<0.001	
Monthly Headache Days across 12 weeks		
Baseline	21.5	21.4
Mean change from baseline	-7.0	-5.1
Difference from placebo	-1.9	
p-value	<0.001	
Monthly Acute Medication Use Days across 12 weeks		
Baseline	15.5	15.4
Mean change from baseline	-6.2	-4.1
Difference from placebo	-2.1	
p-value	<0.001	
≥ 50% MMD Responders across 12 weeks		
% Responders	41	26
Difference from placebo (%)	15	
p-value	<0.001	
MSQ v2.1 RFR Domain* at week 12		
Baseline	43.4	43.9
Mean change from baseline	23.3	17.2
Difference from placebo	6.2	
p-value	<0.001	
AIM-D PDA Domain across 12 weeks**		
Baseline	31.2	29.5
Mean change from baseline	-12.8	-9.4
Difference from placebo	-3.4	
p-value	<0.001	
AIM-D PI Domain* across 12 weeks**		
Baseline	27.1	25.2
Mean change from baseline	-10.6	-7.9
Difference from placebo	-2.7	
p-value	0.003	

* Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score
** Activity Impairment in Migraine-Diary Performance of Daily Activities domain score
*** Activity Impairment in Migraine-Diary Physical Impairment domain score

Figure 5 shows the mean change from baseline in MMD in Study 3. Patients treated with QULIPTA had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo.

Figure 3: Change from Baseline in Monthly Migraine Days in Study 3

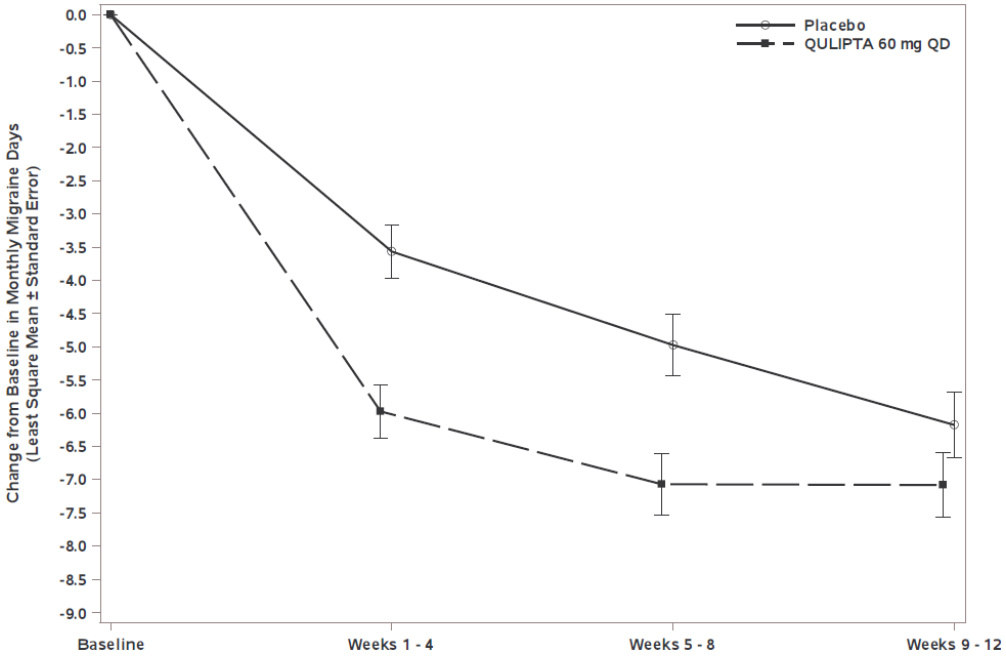
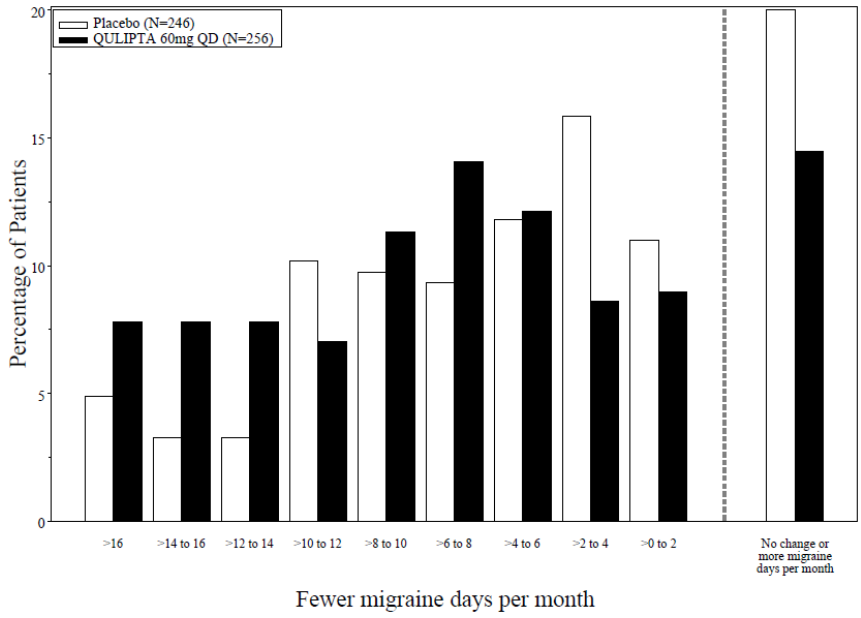


Figure 6 shows the distribution of change from baseline in mean MMD across the 12-week treatment period, in 2-day increments, by treatment group. A treatment benefit of QULIPTA over placebo is seen across a range of mean changes from baseline in MMD.

Figure 4: Distribution of Change from Baseline in Mean Monthly Migraine Days by Treatment Group in Study 3



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

QULIPTA 10 mg is supplied as white to off-white, round biconvex tablets debossed with “A” and “10” on one side in the following packaging presentations:

- Bottle of 30
- Carton box of 4 tablets in blister

QULIPTA 30 mg is supplied as white to off-white, oval biconvex tablets debossed with “A30” on one side in the following packaging presentations:

- Bottle of 30
- Carton box of 4 tablets in blister

QULIPTA 60 mg is supplied as white to off-white, oval biconvex tablets debossed with “A60” on one side in the following packaging presentations:

- Bottle of 30
- Carton box of 4 tablets in blister.

Not all pack sizes may be marketed.

16.2 Storage and Handling

Store below 25°C.

Shelf life after opening:

Bottle pack: discard 59 days after first opening.

The expiry date of the product is indicated on the packaging materials.

17. Manufacturer

Forest Laboratories Ireland Ltd., Clonshaugh Business and Technology Park, Clonshaugh, Dublin 17, D17, E400, Ireland

18. License Holder

Abbvie Biopharmaceuticals Ltd., 4 Haharash st., Hod Hasharon

19. Registration Number

Qulipta 10 mg: 170-61-37169-99
Qulipta 30 mg: 170-62-37170-99
Qulipta 60 mg: 170-63-37171-99

Revised in September 2025.