HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use APONVIE® safely and effectively. See full prescribing information for APONVIE.

APONVIE® (aprepitant) injectable emulsion, for intravenous use
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------

APONVIE is a substance P/neurokinin-1 (NK_1) receptor antagonist, indicated for the prevention of postoperative nausea and vomiting (PONV) in adults.

Limitations of Use:
APONVIE has not been studied for treatment of established nausea and vomiting. (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dose is 32 mg administered as a 30 second intravenous injection prior to induction of anesthesia. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Injectable emulsion: 32 mg/4.4 mL (7.2 mg/mL) in single-dose vial. (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to any component of this product. (4, 5.1)
- Concurrent use with pimozide. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions (including anaphylaxis): May occur during or soon after administration. If symptoms occur, administer appropriate medical therapy. (4, 5.1)
- CYP3A4 Interactions: Aprepitant is a substrate, weak-to-moderate inhibitor, and inducer of CYP3A4; see full prescribing information. (5.2, 7.2)
- Warfarin (a CYP2C9 substrate): Risk of decreased INR of prothrombin time; monitor INR in 2-week period, particularly at 7 to 10 days, following administration of APONVIE. (5.3, 7.1)
- Hormonal Contraceptives: Efficacy of contraceptives may be reduced for 28 days following administration of aprepitant. Use effective alternative or back-up methods of non-hormonal contraception. (5.4, 7.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥3%) are (6.1):

- Single-dose APONVIE: constipation, fatigue, and headache.
- Single-dose oral aprepitant: constipation and hypotension.

To report SUSPECTED ADVERSE REACTIONS, contact Heron Therapeutics, Inc. at 1-844-437-6611 and *www.APONVIE.com* or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

See full prescribing information for a list of clinically significant drug interactions. (4, 5.2, 5.3, 5.4, 7.1, 7.2)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

APONVIE is indicated for the prevention of postoperative nausea and vomiting (PONV) in adults.

Limitations of Use

APONVIE has not been studied for the treatment of established nausea and vomiting.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose in adults of APONVIE is 32 mg administered as a 30 second intravenous injection prior to induction of anesthesia.

2.2 Preparation and Administration

- Inspect the vial for particulate matter and discoloration prior to administration; discard if present. APONVIE is opaque and off-white to amber in color.
- Aseptically withdraw 4.4 mL from the vial.
- Flush the infusion line with normal saline before and after administration of APONVIE.

2.3 Compatibilities

APONVIE is compatible with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, and solutions containing divalent cations (e.g., calcium, magnesium), including Lactated Ringer's Solution.

3 DOSAGE FORMS AND STRENGTHS

Injectable emulsion: 32 mg/4.4 mL (7.2 mg/mL) aprepitant as an opaque, off-white to amber emulsion, in a single-dose vial.

4 CONTRAINDICATIONS

APONVIE is contraindicated in patients:

- with a history of hypersensitivity to aprepitant or any component of the product *[see Description (11)]*. Hypersensitivity reactions have included anaphylaxis *[see Warnings and Precautions (5.1)]*.
- taking pimozide. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of pimozide, which is a CYP3A4 substrate, potentially causing serious or life-threatening reactions, such as QT prolongation, a known adverse reaction of pimozide *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, during or soon after administration of aprepitant have occurred. Symptoms including dyspnea, eye swelling, flushing, pruritus, and wheezing have been reported *[see Adverse Reactions (6.2)]*.

Monitor patients during and after administration. If hypersensitivity reactions occur, administer appropriate medical therapy. Do not administer APONVIE in patients who experience these symptoms with previous use of aprepitant.

5.2 Clinically Significant CYP3A4 Drug Interactions

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4.

- Use of pimozide, a CYP3A4 substrate, with APONVIE is contraindicated *[see Contraindications (4)]*.
- Use of APONVIE with strong CYP3A4 inhibitors (e.g., ketoconazole) may increase plasma concentrations of aprepitant and result in an increased risk of adverse reactions related to APONVIE *[see Drug Interactions (7.2)]*.
- Use of APONVIE with strong CYP3A4 inducers (e.g., rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of APONVIE *[see Drug Interactions (7.2)]*.

5.3 Decrease in INR with Concomitant Warfarin

Use of aprepitant with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the International Normalized Ratio (INR) of prothrombin time *[see Clinical Pharmacology (12.3)]*. Monitor the INR in patients on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following administration of APONVIE *[see Drug Interactions (7.1)]*.

5.4 Risk of Reduced Efficacy of Hormonal Contraceptives

The efficacy of hormonal contraceptives may be reduced for 28 days following administration of APONVIE *[see Clinical Pharmacology (12.3)]*. Advise patients to use effective alternative or back-up methods of non-hormonal contraception for 1 month following administration of APONVIE *[see Drug Interactions (7.1) and Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*

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 clinical practice.

The safety of APONVIE for prevention of PONV was evaluated as a single dose in healthy subjects and established from adequate and well-controlled studies of oral aprepitant *[see Clinical Studies (14)]*. Adverse reactions observed in these studies are described below.

Safety of APONVIE

A total of 51 healthy subjects received a single 32 mg dose of APONVIE as a 30 second intravenous injection. Adverse reactions reported in at least 3% of subjects were constipation (8%), fatigue (6%), and headache (4%).

Safety of Oral Aprepitant

In 2 active-controlled, double-blind clinical studies in patients receiving general anesthesia (Studies 1 and 2), 40 mg oral aprepitant was compared to 4 mg intravenous ondansetron *[see Clinical Studies (14)]*.

There were 564 patients treated with oral aprepitant and 538 patients treated with ondansetron.

The most common adverse reactions reported in patients treated with oral aprepitant for PONV in pooled Studies 1 and 2 are listed in Table 1.

Table 1: Most Common Adverse Reactions in Oral Aprepitant-Treated Patients in a Pooled Analysis of PONV Studies*

	Oral Aprepitant 40 mg (N = 564)	**Ondansetron (N = 538)**
Constipation	9%	8%
Hypotension	6%	5%

*Reported in ≥3% of patients treated with oral aprepitant 40 mg and at a greater incidence than with ondansetron.

In a pooled analysis of PONV studies, less common adverse reactions reported in more than 0.5% of patients treated with oral aprepitant and at a greater incidence than ondansetron were dizziness and urticaria.

In addition, two serious adverse reactions were reported in PONV clinical studies of oral aprepitant in patients taking a higher than recommended dose: one case of constipation, and one case of sub-ileus.

Other Studies

Angioedema, urticaria, and Stevens-Johnson syndrome were reported as serious adverse reactions in patients receiving oral aprepitant in non-PONV studies.

6.2 Postmarketing Experience

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

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria, Stevens-Johnson syndrome/toxic epidermal necrolysis *[see Warnings and Precautions (5.1)]*.

Immune system disorders: hypersensitivity reactions including anaphylaxis and anaphylactic shock *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Nervous system disorders: ifosfamide-induced neurotoxicity reported after aprepitant and ifosfamide coadministration.

7 DRUG INTERACTIONS

7.1 Effect of Aprepitant on the Pharmacokinetics of Other Drugs

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9 *[see Clinical Pharmacology (12.3)]*.

Table 2 includes drug interactions affecting drugs co-administered with APONVIE and instructions for preventing or managing them.

Table 2: Drug Interactions Affecting Drugs When Co-Administered with APONVIE

Pimozide	
Clinical Impact	Increased pimozide exposure.
Intervention	APONVIE is contraindicated *[see Contraindications (4)]*.
Hormonal Contraceptives	
Clinical Impact	Decreased hormonal exposure for 28 days after administration of APONVIE *[see Warnings and Precautions (5.3), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)]*.
Intervention	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used for 1 month following administration of APONVIE.
Examples	birth control pills, transdermal systems, implants, and certain intrauterine systems
CYP2C9 Substrates	
Warfarin	
Clinical Impact	Decreased warfarin exposure and decreased prothrombin time (INR) *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.
Intervention	In patients on chronic warfarin therapy, monitor prothrombin time (INR) in the 2-week period, particularly at 7 to 10 days, following administration of APONVIE.
Other Antiemetic Agents	
5-HT$_3$ Antagonists	
Clinical Impact	No change in the exposure of the 5-HT$_3$ antagonist *[see Clinical Pharmacology (12.3)]*.
Intervention	No dosage adjustment needed.
Examples	ondansetron, granisetron, dolasetron
Corticosteroids	
Clinical Impact	No clinically significant change in the exposure of dexamethasone or methylprednisolone *[see Clinical Pharmacology (12.3)]*.
Intervention	No dosage adjustment needed.

7.2 Effect of Other Drugs on the Pharmacokinetics of Aprepitant

Aprepitant is a CYP3A4 substrate *[see Clinical Pharmacology (12.3)]*. Table 3 includes drug interactions affecting APONVIE when co-administered with other drugs and instructions for preventing them.

Table 3: Drug Interactions Affecting APONVIE When Co-Administered with Other Drugs

Strong CYP3A4 Inhibitors	
Clinical Impact	Significantly increased exposure of aprepitant may increase the risk of adverse reactions associated with APONVIE *[see Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of APONVIE.
Examples	ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir
Strong CYP3A4 Inducers	
Clinical Impact	Substantially decreased exposure of aprepitant in patients chronically taking a strong CYP3A4 inducer may decrease the efficacy of APONVIE *[see Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of APONVIE.
Examples	rifampin, carbamazepine, phenytoin

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on aprepitant use in pregnant women to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Avoid use of APONVIE in pregnant women due to the alcohol content *(see Clinical Considerations)*. In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic drug concentrations (area under the plasma-concentration time curve [AUC]) of oral aprepitant approximately 4.8 times the exposure at the recommended human dose of APONVIE *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

APONVIE contains alcohol. Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development. There is no safe level of alcohol exposure in pregnancy; therefore, avoid use of APONVIE in pregnant women.

Data

Animal Data

In embryofetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis at oral doses up to 1000 mg/kg twice daily (rats) and up to the maximum tolerated dose of 125 mg/kg/day (rabbits). No embryofetal lethality or malformations were observed at any dose level in either species. The exposures (AUC) in pregnant rats at 1000 mg/kg twice daily and in pregnant rabbits at 125 mg/kg/day were approximately 4.8 times the exposure at the recommended human dose of APONVIE. Aprepitant crosses the placenta in rats and rabbits.

8.2 Lactation

Risk Summary

There are no data on the presence of aprepitant in human milk, the effects on the breastfed infant, or the effects on milk production. Aprepitant is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for APONVIE and any potential adverse effects on the breastfed infant from APONVIE or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Upon administration of APONVIE, the efficacy of hormonal contraceptives may be reduced. Advise females of reproductive potential using hormonal contraceptives to use an effective alternative or back-up non-hormonal contraceptive (such as condoms or spermicides) for 1 month following administration of APONVIE *[see Warnings and Precautions (5.4), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of APONVIE have not been established in pediatric patients.

Juvenile Animal Study

A study was conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Rats were treated at oral doses up to the maximum feasible dose of 1000 mg/kg twice daily from the early postnatal period (Postnatal Day 10) through Postnatal Day 58. Slight changes in the onset of sexual maturation were observed in female and male rats; however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

8.5 Geriatric Use

Of the 1120 adult patients treated with oral aprepitant in PONV clinical studies, 7% were aged 65 and over, while 2% were aged 75 and over. Clinical studies of aprepitant did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. No clinically meaningful differences in the

pharmacokinetics of oral aprepitant were observed in healthy geriatric subjects compared to younger adult subjects *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Headache, fatigue, and dizziness were reported in healthy subjects receiving a single dose of 100 or 130 mg aprepitant injectable emulsion (3.1 to 4 times the recommended dose).

Drowsiness and headache were reported in one patient who ingested 1440 mg of oral aprepitant.

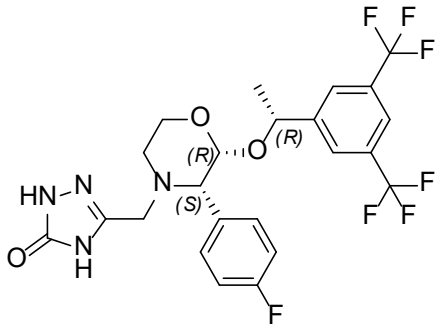
In the event of overdose, general supportive treatment and monitoring should be provided.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

APONVIE injectable emulsion contains the active ingredient, aprepitant. Aprepitant is a substance P/neurokinin 1 (NK_1) receptor antagonist, an antiemetic agent, and chemically described as 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Its empirical formula is $C_{23}H_{21}F_7N_4O_3$, and its structural formula is:



Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

APONVIE (aprepitant) injectable emulsion is a sterile, opaque, off-white to amber liquid in a single-dose vial for intravenous use. Each vial contains 32 mg aprepitant in 4.4 mL of emulsion. The emulsion also contains the following inactive ingredients: dehydrated alcohol (125 mg), egg lecithin (636 mg), sodium oleate (21 mg), soybean oil (424 mg), sucrose (238 mg), and water for injection (2968 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin ($5\text{-}HT_3$), dopamine, and corticosteroid receptors, the targets of existing therapies for postoperative nausea and vomiting (PONV). Aprepitant has been shown in animal models to inhibit emesis via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK_1 receptors.

12.2 Pharmacodynamics

NK_1 Receptor Occupancy

In two single-blind, multiple-dose, randomized, and placebo-controlled studies, healthy young men received oral aprepitant doses of 10 mg (N=2), 30 mg (N=3), 100 mg (N=3), or 300 mg (N=5) once daily (0.08, 0.24, 0.8, and 2.4 times a single 125 mg dose of oral aprepitant, respectively) for 14 days with 2 or 3 subjects on placebo. Both plasma aprepitant concentration and NK_1 receptor occupancy in the corpus striatum by PET were evaluated, at predose and 24 hours after the last dose. At aprepitant plasma concentrations of approximately 10 ng/mL and 100 ng/mL, the NK_1 receptor occupancies were approximately 50% and 90%, respectively. The oral aprepitant regimen produced mean trough plasma aprepitant concentrations greater than 500 ng/mL in adults, which would be expected to, based on the fitted curve with the Hill equation, result in greater than 95% brain NK_1 receptor occupancy. However, the receptor occupancy for the PONV dosing regimen has not been determined. In addition, the relationship between NK_1 receptor occupancy and the clinical efficacy of aprepitant has not been established.

Cardiac Electrophysiology

In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200 mg intravenous dose of fosaprepitant, a prodrug of aprepitant, had no effect on the QTc interval. QT prolongation with the recommended APONVIE dosing regimen is not expected.

12.3 Pharmacokinetics

Absorption

Following administration of a single intravenous 32 mg dose of APONVIE administered as a 30 second injection to healthy subjects, mean (CV%) area under the plasma concentration-time curve ($AUC_{0-\infty}$) was 7.8 (27.4%) mcg·hr/mL and mean plasma concentration at 5 minutes post-dose was 2.1 (19%) mcg/mL.

In healthy subjects, a single dose of 32 mg of APONVIE administered as a 30 second intravenous injection resulted in a 13% higher $AUC_{0-\infty}$ of aprepitant compared to a single oral dose of 40 mg aprepitant, which was not considered clinically meaningful.

Distribution

Aprepitant was greater than 99% bound to plasma proteins. The mean volume of distribution following APONVIE administration was approximately 72 L in healthy subjects.

Aprepitant crossed the blood-brain barrier in humans *[see Clinical Pharmacology (12.1)]*.

Elimination

Metabolism

Aprepitant underwent extensive metabolism. In vitro studies using human liver microsomes indicated that aprepitant was metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism was largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected.

In healthy young adults, aprepitant accounted for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300 mg dose of [^{14}C]-aprepitant, indicating a

substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which were only weakly active, had been identified in human plasma.

Excretion

Aprepitant was eliminated primarily by metabolism; aprepitant was not renally excreted. The mean terminal half-life of aprepitant following administration of APONIVE was 12 hours. The mean plasma clearance of aprepitant was 4.4 L/h.

Specific Populations

Geriatric Patients

Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in healthy elderly subjects (65 years and older) relative to younger adult subject. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in healthy elderly subjects relative to younger adult subjects. These differences are not considered clinically meaningful *[see Use in Specific Populations (8.5)]*.

Male and Female Patients

Following oral administration of a single dose of aprepitant ranging from 40 mg to 375 mg, the $AUC_{0\text{-}24hr}$ and C_{max} are 9% and 17% higher in females as compared with males. The half-life of aprepitant was approximately 25% lower in females as compared with males. These differences are not considered clinically meaningful.

Racial or Ethnic Groups

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the $AUC_{0\text{-}24hr}$ and C_{max} were approximately 27% and 19% higher in Hispanics as compared with Caucasians. The $AUC_{0\text{-}24hr}$ and C_{max} were 74% and 47% higher in Asians as compared to Caucasians. There was no difference in $AUC_{0\text{-}24hr}$ or C_{max} between Caucasians and Blacks. These differences are not considered clinically meaningful.

Patients with Renal Impairment

A single 240 mg oral dose of aprepitant was administered to patients with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m^2 as measured by 24-hour urinary creatinine clearance) and to patients with end stage renal disease (ESRD) requiring hemodialysis. In patients with severe renal impairment, the $AUC_{0\text{-}\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects (creatinine clearance greater than 80 mL/min estimated by Cockcroft-Gault method). In patients with ESRD undergoing hemodialysis, the $AUC_{0\text{-}\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

No clinically meaningful changes in the pharmacokinetics of aprepitant are expected in patients with any degree of renal impairment following administration of a single dose of APONVIE 32 mg as an intravenous injection.

Patients with Hepatic Impairment

Following administration of a single 125 mg oral dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic impairment (Child-Pugh score 5 to 6), the $AUC_{0\text{-}24hr}$ of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic impairment (Child Pugh score 7 to 9), the $AUC_{0\text{-}24hr}$ of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in $AUC_{0\text{-}24hr}$ are not considered clinically meaningful.

No clinically meaningful changes in the pharmacokinetics of aprepitant are expected in patients with mild or moderate hepatic impairment following administration of a single dose of APONVIE 32 mg as an intravenous injection. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9).

Body Mass Index (BMI)

For every 5 kg/m^2 increase in BMI, $AUC_{0\text{-}24hr}$ and C_{max} of aprepitant decrease by 9% and 10%. BMI of subjects in the analysis ranged from 18 kg/m^2 to 36 kg/m^2. This change is not considered clinically meaningful.

Drug Interactions Studies

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter.

Aprepitant acts as a weak inhibitor of CYP3A4 when administered as a single intravenous 32 mg dose of APONVIE.

Effects of Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates:

Midazolam: Oral aprepitant 40 mg administered as a single oral dose on Day 1 increased the AUC of oral midazolam 2 mg by approximately 1.2-fold on Day 1. This effect was not considered clinically meaningful.

Corticosteroids:

Dexamethasone: A single dose of oral aprepitant 40 mg when coadministered with a single dose of dexamethasone 20 mg, increased the AUC of dexamethasone by 1.45-fold, which is not considered clinically meaningful.

Methylprednisolone: Although the concomitant administration of methylprednisolone with the single 40 mg dose of oral aprepitant has not been studied, a single 40 mg dose of oral aprepitant produces a weak inhibition of CYP3A4 (based on midazolam interaction study) and it is not expected to alter the plasma concentrations of methylprednisolone to a clinically meaningful degree.

CYP2C9 substrates:

Warfarin: A single 125 mg dose of oral aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to subjects who were stabilized on chronic warfarin therapy. Although there was no effect of oral aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with oral aprepitant *[see Drug Interactions (7.1)]*.

Tolbutamide: Oral aprepitant, when given as a 40 mg single dose on Day 1, decreased the AUC of tolbutamide by 8% on Day 2, 16% on Day 4, 15% on Day 8, and 10% on Day 15, when a single dose of tolbutamide 500 mg was administered prior to the administration of oral aprepitant 40 mg and on Days 2, 4, 8, and 15. This effect was not considered clinically meaningful.

Other Drugs:

Oral contraceptives: When a daily dosage of an oral contraceptive containing ethinyl estradiol and norgestimate was administered on Days 1 through 21, and oral aprepitant 40 mg was given on Day 8, the AUC of ethinyl estradiol decreased by 4% and by 29% on Day 8 and Day 12, respectively, while the AUC of norelgestromin increased by 18% on Day 8 and decreased by 10% on Day 12. In addition, the trough concentrations of ethinyl estradiol and norelgestromin on Days 8 through 21 were generally lower following coadministration of the oral contraceptive with oral aprepitant 40 mg on Day 8 compared to the trough levels following administration of the oral contraceptive alone *[see Drug Interactions (7.1)]*.

P-glycoprotein substrates: Aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin in a clinical drug interaction study.

5-HT_3 antagonists: In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Effect of Other Drugs on the Pharmacokinetics of Aprepitant

Rifampin: When a single 375 mg dose of oral aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold *[see Drug Interactions (7.2)]*.

Ketoconazole: When a single 125 mg dose of oral aprepitant was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold *[see Drug Interactions (7.2)]*.

Diltiazem: In a study in 10 subjects with mild to moderate hypertension, administration of 100 mg of fosaprepitant, a prodrug of aprepitant, as an intravenous infusion with 120 mg of diltiazem, a moderate CYP3A4 inhibitor administered three times daily, resulted in a

1.5-fold increase in the aprepitant AUC and a 1.4-fold increase in the diltiazem AUC. This effect was not considered clinically meaningful.

When fosaprepitant was administered with diltiazem, the mean maximum decrease in diastolic blood pressure was greater than that observed with diltiazem alone (24.3 ± 10.2 mm Hg with fosaprepitant versus 15.6 ± 4.1 mm Hg without fosaprepitant). The mean maximum decrease in systolic blood pressure was also greater after co-administration of diltiazem with fosaprepitant than administration of diltiazem alone (29.5 ± 7.9 mm Hg with fosaprepitant versus 23.8 ± 4.8 mm Hg without fosaprepitant). Co-administration of fosaprepitant and diltiazem, however, did not result in any additional clinically meaningful changes in heart rate or PR interval, beyond those changes observed with diltiazem alone.

Paroxetine: Coadministration of once daily doses of oral aprepitant 85 mg or 170 mg, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine. This effect was not considered clinically meaningful.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced systemic exposures to aprepitant (AUC) approximately 5.1 times the human exposure from APONVIE 32 mg. Treatment with aprepitant at doses of 5 to 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure approximately 11.5 times the human exposure at the recommended human dose of APONVIE. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice.

Mutagenesis

Aprepitant was not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test, and the mouse micronucleus test.

Impairment of Fertility

Oral aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male and female rats higher than the exposure at the recommended human dose of APONVIE).

14 CLINICAL STUDIES

The safety and efficacy of APONVIE have been established based on adequate and well-controlled studies of a single-dose of oral aprepitant in adults. Below is a description of the results of these adequate and well-controlled studies of oral aprepitant for the prevention of PONV.

In two multicenter, randomized, double-blind, active comparator-controlled, parallel-group clinical studies (Studies 1 and 2), oral aprepitant was compared with ondansetron for the prevention of postoperative nausea and vomiting in 1658 patients undergoing open abdominal surgery. These two studies were of similar design; however, they differed in terms of study hypothesis, efficacy analyses, and geographic location. Study 1 was a multinational study including the U.S., whereas, Study 2 was conducted entirely in the U.S.

In the two studies, patients were randomized to receive 40 mg oral aprepitant, 125 mg oral aprepitant, or 4 mg intravenous ondansetron as a single dose. Aprepitant was given orally with 50 mL of water 1 to 3 hours before anesthesia. Ondansetron was given intravenously immediately before induction of anesthesia. A comparison between the oral aprepitant 125 mg dose did not demonstrate any additional clinical benefit over the oral 40 mg dose.

Of the 564 patients who received 40 mg oral aprepitant, 92% were women and 8% were men; of these, 58% were White, 13% Hispanic American, 7% Multi-Racial, 14% Black, 6% Asian, and 2% Other. The age of patients treated with 40 mg oral aprepitant ranged from 19 to 84 years, with a mean age of 46.1 years. 46 patients were 65 years or older, with 13 patients being 75 years or older.

The antiemetic activity of oral aprepitant was evaluated during the 0 to 48 hour period following the end of surgery.

Efficacy measures in Study 1 included:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- complete response (defined as no emetic episodes and no use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 48 hours following the end of surgery (secondary)
- time to first use of rescue medication in the 0 to 24 hours following the end of surgery (exploratory)
- time to first emesis in the 0 to 48 hours following the end of surgery (exploratory)

A closed testing procedure was applied to control the type I error for the primary endpoints.

The results of the primary and secondary endpoints for 40 mg oral aprepitant and 4 mg ondansetron are described in Table 4.

Table 4: Response Rates for Select Efficacy Endpoints (Modified-Intention-to-Treat Population) – Study 1

Treatment	n/N (%)	Oral Aprepitant vs. Ondansetron		
		Difference[a]	Odds Ratio[b]	Analysis
PRIMARY ENDPOINTS				
No Vomiting 0 to 24 hours (Superiority) (no emetic episodes)				
Oral aprepitant 40 mg	246/293 (84.0)	12.6%	2.1	P<0.001[c]
Ondansetron	200/280 (71.4)			
Complete Response (Non-inferiority: If LB[d] >0.65) (no emesis and no rescue therapy, 0 to 24 hours)				
Oral aprepitant 40 mg	187/293 (63.8)	8.8%	1.4	LB=1.02
Ondansetron	154/280 (55.0)			
Complete Response (Superiority: If LB >1.0) (no emesis and no rescue therapy, 0 to 24 hours)				
Oral aprepitant 40 mg	187/293 (63.8)	8.8%	1.4	LB=1.02[d]
Ondansetron	154/280 (55.0)			
SECONDARY ENDPOINT				
No Vomiting 0 to 48 hours (Superiority) (no emetic episodes)				
Oral aprepitant 40 mg	238/292 (81.5)	15.2%	2.3	P<0.001[e]
Ondansetron	185/279 (66.3)			

n/N = Number of responders/number of patients in analysis.

[a] Difference (%): oral aprepitant 40 mg minus ondansetron.

[b] Estimated odds ratio for oral aprepitant versus ondansetron. A value of >1 favors aprepitant over ondansetron.

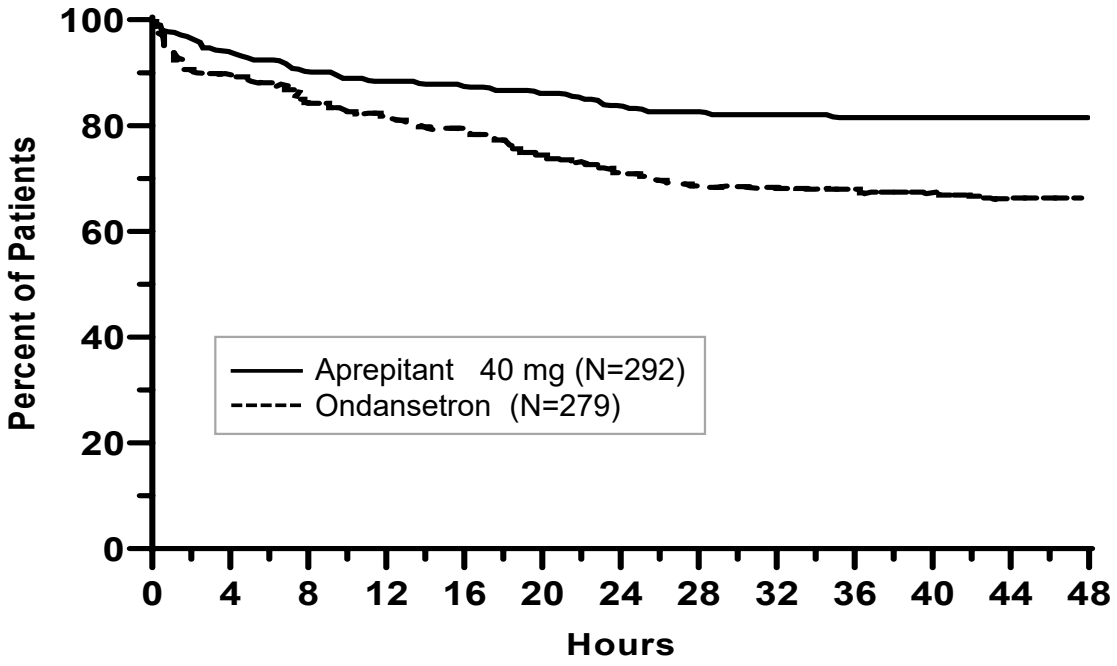
[c] P-value of two-sided test <0.05.

[d] LB = lower bound of 1-sided 97.5% confidence interval for the odds ratio.

[e] Based on the prespecified fixed sequence multiplicity strategy, oral aprepitant 40 mg was not superior to ondansetron.

In Study 1, the use of oral aprepitant did not affect the time to first use of rescue medication when compared to ondansetron. However, compared to the ondansetron group, use of oral aprepitant delayed the time to first vomiting, as depicted in Figure 1.

Figure 1: Percent of Patients Who Remain Emesis Free During the 48 Hours Following End of Surgery in Study 1



Efficacy measures in Study 2 included:

- complete response (defined as no emetic episodes and no use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 24 hours following the end of surgery (secondary)
- no use of rescue therapy in the 0 to 24 hours following the end of surgery (secondary)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 48 hours following the end of surgery (secondary)

Study 2 failed to satisfy its primary hypothesis that oral aprepitant is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery.

The study demonstrated that 40 mg oral aprepitant had a clinically meaningful effect with respect to the secondary endpoint “no vomiting” during the first 24 hours after surgery and was associated with a 16% improvement over ondansetron for the no vomiting endpoint (Table 5).

Table 5: Response Rates for Select Efficacy Endpoints (Modified-Intention-to-Treat Population) – Study 2

Treatment	n/N (%)	Oral Aprepitant vs. Ondansetron		
		Difference[a]	Odds Ratio[b]	Analysis
PRIMARY ENDPOINT				
Complete Response (no emesis and no rescue therapy, 0 to 24 hours)				
Oral aprepitant 40 mg	111/248 (44.8)	2.5%	1.1	0.61
Ondansetron	104/246 (42.3)			
SECONDARY ENDPOINTS				
No Vomiting (no emetic episodes, 0 to 24 hours)				
Oral aprepitant 40 mg	223/248 (89.9)	16.3%	3.2	<0.001[c]
Ondansetron	181/246 (73.6)			
No Use of Rescue Medication (for established emesis or nausea, 0 to 24 hours)				
Oral aprepitant 40 mg	112/248 (45.2)	-0.7%	1.0	0.83
Ondansetron	113/246 (45.9)			
No Vomiting 0 to 48 hours (Superiority) (no emetic episodes, 0 to 48 hours)				
Oral aprepitant 40 mg	209/247 (84.6)	17.7%	2.7	<0.001[c]
Ondansetron	164/245 (66.9)			

n/N = Number of responders/number of patients in analysis.

[a] Difference (%): oral aprepitant 40 mg minus ondansetron.

[b] Estimated odds ratio: oral aprepitant 40 mg versus ondansetron.

[c] Not statistically significant after prespecified multiplicity adjustment.

16 HOW SUPPLIED/STORAGE AND HANDLING

APONVIE injectable emulsion is supplied as an opaque, off-white to amber emulsion in a single-dose glass vial containing 32 mg/4.4 mL (7.2 mg/mL) aprepitant:

NDC 47426-401-10 10 single-dose vials (NDC 47426-401-01) per carton

Storage

Refrigerate APONVIE at 2°C to 8°C (36°F to 46°F).

APONVIE can remain at room temperature 20°C to 25°C (68°F to 77°F) up to 60 days.

Do not freeze.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity

Advise patients that hypersensitivity reactions, including anaphylaxis, have been reported with aprepitant *[see Warnings and Precautions (5.1)]*. Advise patients to seek immediate medical attention if they experience signs or symptoms of a hypersensitivity reaction, such as hives, rash and itching, skin peeling or sores, or difficulty in breathing or swallowing, or dizziness, rapid or weak heartbeat or feeling faint.

Drug Interactions

Advise patients to discuss all medications they are taking, including other prescription, non-prescription medication or herbal products *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

Warfarin: Instruct patients on chronic warfarin therapy to follow instructions from their healthcare provider regarding blood draws to monitor their INR during the 2-week period, particularly at 7 to 10 days, following administration of APONVIE *[see Warnings and Precautions (5.3)]*.

Hormonal Contraceptives: Advise patients that administration of APONVIE may reduce the efficacy of hormonal contraceptives. Instruct patients to use effective alternative or back-up methods of non-hormonal contraception (such as condoms or spermicides) for 1 month following administration of APONVIE *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.3)]*.

Pregnancy

Advise pregnant women of the potential risk to a fetus and to avoid use of APONVIE during pregnancy *[see Use in Specific Populations (8.1)]*.

Manufactured for: Heron Therapeutics, Inc., Cary, NC 27511

Patent: https://www.herontx.com/patents/

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