APONVIE™
(aprepitant) injectable emulsion

PRODUCT MONOGRAPH

INDICATION 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.

IMPORTANT SAFETY INFORMATION

Contraindications:

APONVIE is contraindicated in patients with a history of hypersensitivity to aprepitant or any component of the product, and in patients taking pimozide. Increased pimozide levels may cause serious or life-threatening reactions, such as QT prolongation.

Please see Important Safety Information throughout and full Prescribing Information.

APONVIE™
(aprepitant) injectable emulsion

TABLE OF CONTENTS

Please see Important Safety Information throughout and full Prescribing Information.

EXECUTIVE SUMMARY

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.

APONVIE is the first and only IV NK_1 antagonist for the prevention of PONV, delivered via a single IV push. The active ingredient in APONVIE is aprepitant, which demonstrates superior vomiting prevention versus standard-of-care IV ondansetron after surgery in both the 24-and 48-hour timeframes.[1-3,a]

The approval of APONVIE in the United States via 505(b)2 pathway is supported by 2 Phase 3 randomized, double-blind, active comparator-controlled, parallel-group clinical studies of patients undergoing abdominal surgery. In a Phase 1 bioequivalence study, APONVIE has demonstrated bioequivalence to oral aprepitant. APONVIE has a similar pharmacokinetic profile to oral aprepitant, though the IV administration allows for higher plasma concentrations and an earlier median time to maximum concentration than oral administration.[4]

Oral aprepitant has been used for PONV since 2006.[5] In 2 studies of more than 560 patients undergoing general anesthesia, there were no significant differences in the incidence of adverse events between oral aprepitant and IV ondansetron.[1-3] Aprepitant is not associated with QT prolongation, urinary retention, blurred vision, cognitive issues including sedation, or instances of serotonin syndrome.[1] Aprepitant is well tolerated, with an established safety profile. IV aprepitant has been administered, even at a higher dose (130 mg), in more than 2.5 million doses to treat chemotherapy-induced nausea and vomiting.[6]

[a]Unadjusted *P* value.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

BACKGROUND AND UNMET NEED

Postoperative nausea and vomiting are 2 of the most common adverse events following surgery, with an estimated incidence of **more than 30%** in the general surgical population and **up to 80% in high-risk patients.**[7]

Ondansetron, one of the most commonly used antiemetics, has a relatively short half-life (3 to 6 hours). Even when treated with ondansetron or other antiemetics, more than 30% of patients still experience postoperative nausea and vomiting.[2,8]

Patients at moderate-to-high risk of PONV exhibit the following traits[7]:

- Females
- Non-smokers
- Younger age
- Patients with a history of PONV or motion sickness
- Patients undergoing general anesthesia
- Patients who are treated with opioids

A commonly used risk score for patients undergoing anesthesia is the simplified Apfel risk score, which is based on 4 predictors: **female sex, history of PONV and/or motion sickness, nonsmoking status, and use of postoperative opioids.**[7]

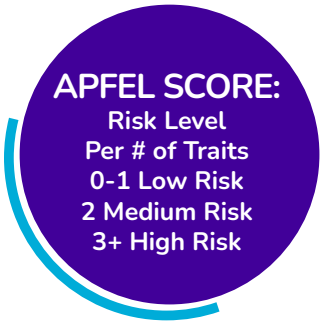
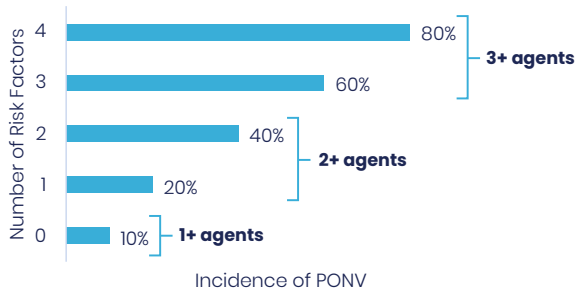


Figure 1. Apfel Score[7]



PONV can be highly distressing and is a major cause of patient dissatisfaction after surgery, with patients ranking vomiting as the most undesirable outcome when asked about postsurgical complications.[9] Poorly managed PONV can also affect a patient's overall length of hospital stay and may require unanticipated hospital readmission, which can lead to increased cost to the patient and to the healthcare system.[10-12] Clinical complications of persistent retching or vomiting can include aspiration, tension on suture lines, development of hematomas beneath surgical flaps, and electrolyte abnormalities and dehydration.[12,13]

Enhanced recovery after surgery (ERAS) protocols include evidence-based practices to improve patient outcomes, including reduced opioid consumption, decreased PONV, and decreased length of stay.[14]

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

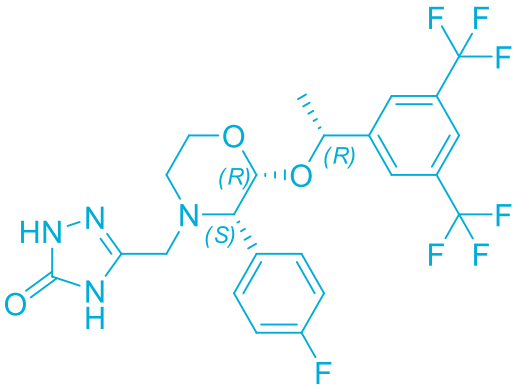
Clinically Significant CYP3A4 Drug Interactions: Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Use of pimozide, a CYP3A4 substrate, with APONVIE is contraindicated. Use of APONVIE with strong CYP3A4 inhibitors (eg, ketoconazole) may increase plasma concentrations of aprepitant and result in an increased risk of adverse reactions related to APONVIE. Use of APONVIE with strong CYP3A4 inducers (eg, rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of APONVIE.

APONVIE™
(aprepitant) injectable emulsion

PRODUCT DESCRIPTION[1]

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 $C_{23}H_{21}F_7N_4O_3$.

Figure 2. APONVIE Structural Formula



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 (0.13 g), egg lecithin (0.64 g), sodium oleate (0.02 g), soybean oil (0.42 g), sucrose (0.24 g), and water for injection (2.97 g).

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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. Monitor the INR in patients on chronic warfarin therapy in the 2-week period particularly at 7 to 10 days, following administration of APONVIE.

CLINICAL PHARMACOLOGY

Mechanism of Action

Substance P, a regulatory peptide that is the preferred endogenous ligand at NK_1 receptors, is found in the gastrointestinal tract (vagal afferents) and areas of the central nervous system thought to be involved in the vomiting reflex (including the nucleus tractus solitarii and area postrema).[3] Substance P binds to NK_1 receptors, inducing nausea or vomiting.[15]

The NK_1 receptors are in the final common pathway to vomiting.[16,17]

One study shows that patients who experience PONV are more likely to have elevated levels of substance P.[15]

Figure 3. The PONV Receptor Pathways[16,17]

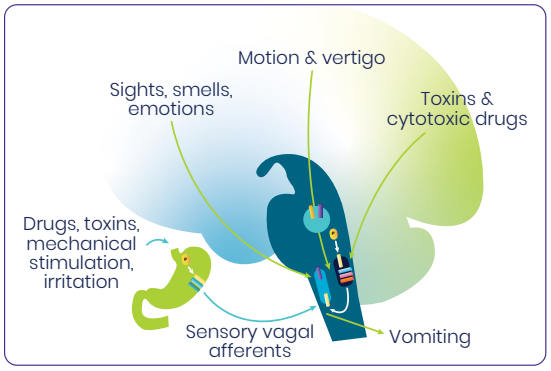
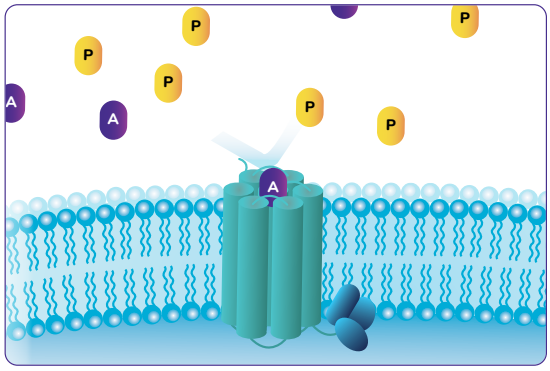


Figure 4. APONVIE binds to NK_1 receptors, blocking substance P[1]



The active ingredient in APONVIE, aprepitant, is a highly selective NK_1 antagonist with clinical efficacy against emesis and a longer half-life than other products approved for PONV. APONVIE crosses the blood-brain barrier and binds to NK_1 receptors with high affinity, blocking substance P and preventing nausea and vomiting.[1]

APONVIE has little or no affinity for serotonin (5-HT3), dopamine, and corticosteroid receptors, the targets of other therapies for postoperative nausea and vomiting (PONV).[1]

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

Risk of Reduced Efficacy of Hormonal Contraceptives: The efficacy of hormonal contraceptives may be reduced for 28 days following administration of APONVIE. Advise patients to use effective alternative or back-up methods of non-hormonal contraception for 1 month following administration of APONVIE.

Pharmacokinetics

APONVIE is administered via **a 30-second IV push**. Therapeutic plasma concentrations associated with **≥97% receptor occupancy in the brain are achieved within 5 minutes** for APONVIE—unlike oral aprepitant, which was taken 1 to 3 hours prior to induction of general anesthesia in clinical trials and does not reach maximum concentration until 3 hours after administration.[1,18-20] **Plasma concentrations of aprepitant with APONVIE were higher than those of the oral formulation for approximately 3 hours**. By the 4-hour timepoint, the plasma concentrations for the 2 formulations converged and remained similar. **At 48 hours, therapeutic plasma concentrations associated with NK_1 receptor occupancy is estimated to be maintained at >90%.**[4,18]

IV administration allows the drug to enter directly into systemic circulation without the delay associated with absorption processes. This results in 100% bioavailability, making it the best way to deliver a drug rapidly and accurately, and bypassing first-pass metabolism.[21]

The expected receptor occupancy draws on modeling from the 2012 Van Laere study, which evaluated the magnitude and duration of brain NK_1 receptor occupancy over a period of 5 days after a single dose of fosaprepitant (a prodrug of aprepitant) 150 mg administered as a 20-minute IV infusion or a single dose of oral aprepitant 165 mg in 16 healthy male subjects. Brain NK_1 receptor occupancy rates were measured using PET imaging and a specific NK_1 receptor binding ligand, which was used to measure displacement by aprepitant. PET scans were conducted before dosing, at T_{max} and 24, 48, and 120 hours post dose. More frequent PK blood samples were collected over 120 hours. While the concentrations of IV fosaprepitant were higher than oral aprepitant for the initial hours, the concentrations were similar thereafter over 120 hours. The brain NK_1 receptor occupancy over 120 hours was also comparable. **An estimated ≥97% receptor occupancy was achieved with plasma concentrations of ≥225 ng/mL.** The authors concluded that IV fosaprepitant 150 mg and oral aprepitant 165 mg are pharmacodynamically equivalent.[19] The relationship between receptor occupancy and efficacy has not been established.

Figure 5. Mean Aprepitant Plasma Concentration[4]

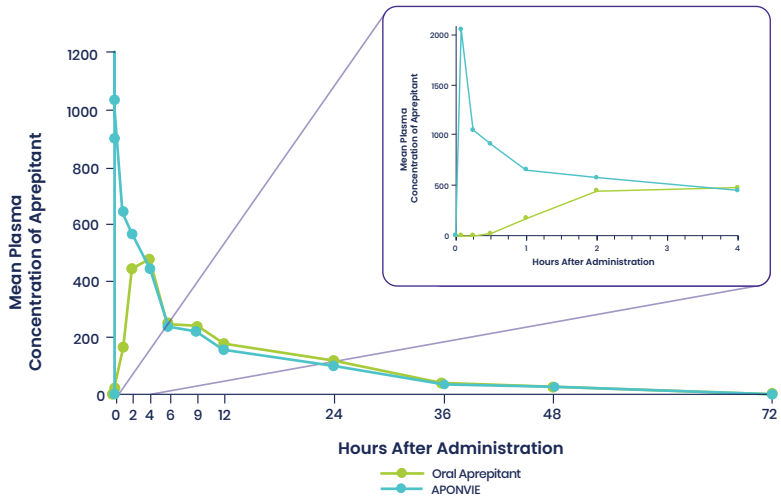


Figure 5 illustrates data from a clinical trial, which demonstrated that APONVIE behaves predictably in the human body and shows bioequivalence given overall exposure to oral aprepitant 40 mg.[4]

IMPORTANT SAFETY INFORMATION

Use in Specific Populations

Avoid use of APONVIE in pregnant women as alcohol is an inactive ingredient in APONVIE. There is no safe level of alcohol exposure in pregnancy.

Pharmacokinetics (CONT)

As expected, due to IV administration of APONVIE, plasma concentrations (C_{max}) of aprepitant were higher than those of the oral formulation for approximately 3 hours.[4]

Table 1. Difference in Plasma Concentrations in the Initial Hours Following Administration[4]

Time after administration (minutes)	*Difference in Plasma Concentration (ng/mL)*
5	2063
15	1055
30	892.11
60	485.2
120	136.4

By the 4-hour timepoint, the plasma concentrations for the 2 formulations converged and remained similar.[4]

Distribution[1]

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

Aprepitant crossed the blood-brain barrier in humans.

Elimination[1]

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 APONVIE was 12 hours. The mean plasma clearance of aprepitant was 4.4 L/h.

IMPORTANT SAFETY INFORMATION

Adverse Reactions

Most common adverse reactions (incidence ≥3%) for APONVIE are constipation, fatigue, and headache and for oral aprepitant are constipation and hypotension.

Report side effects to Heron at 1-844-437-6611 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Pharmacodynamics[1]

NK_1 Receptor Occupancy

In 2 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.

Bioequivalence Study Data[4]

The pharmacokinetics of aprepitant following administration of APONVIE 32 mg as a 30-second IV injection or following oral administration of aprepitant 40 mg were evaluated in a Phase 1 bioequivalence study. This table presents a summary of the PK parameters for aprepitant for APONVIE and oral aprepitant pooled across both studies.

Table 2. Summary of Plasma Pharmacokinetic Parameters

Treatment	*n*[a]	T_{max} *(h)*	C_{max} *(ng/mL)*	AUC_{last} *(h·ng/mL)*	AUC_{inf} *(h·ng/mL)*
A single dose of APONVIE 32 mg 30-second IV injection	31	0.08444 (0.0833-0.105)	2,029 (21.4)	6,748 (30.3)	7,225 (28.4)
A single dose of oral aprepitant 40 mg	32	4.002 (2.00-6.00)	542.3 (46.5)	6,635 (35.1)	7,152 (33.1)

[a]One subject in Study 111 was excluded from the APONVIE treatment due to an atypical PK profile for APONVIE. AUC_{inf} was not reportable for 2 subjects (one from each treatment group) because they failed to meet the inclusion criteria.
Note: Values are presented as mean (%CV) for all parameters except for T_{max}, for which median (range) is presented.

As seen in the table above, the AUC_{last} and AUC_{inf} were comparable for APONVIE 32 mg administered as a 30-second IV injection and oral aprepitant 40 mg.

IMPORTANT SAFETY INFORMATION

Contraindications

APONVIE is contraindicated in patients with a history of hypersensitivity to aprepitant or any component of the product, and in patients taking pimozide. Increased pimozide levels may cause serious or life-threatening reactions, such as QT prolongation.

DOSAGE AND ADMINISTRATION[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.

Preparation

To prepare APONVIE for administration, aseptically withdraw 4.4 mL from the vial. Do not dilute. Flush the infusion line with normal saline before and after administration of APONVIE.

Packaging and Storage

APONVIE is packaged in cartons of 10 5-mL vials, each filled with a single 32-mg dose. APONVIE should be refrigerated for storage (2°C to 8°C or 36°F to 46°F), but can remain at room temperature (20°C to 25°C or 68°F to 77°F) for up to 60 days.

CLINICAL EFFICACY

Phase 3 Clinical Trials[1-3]

APONVIE demonstrated bioequivalence to oral aprepitant in a clinical trial.

In 2 Phase 3, multicenter, randomized, double-blind, active comparator-controlled, parallel-group clinical studies, an oral formulation of aprepitant was compared with IV ondansetron for the prevention of postoperative nausea and vomiting in patients undergoing open abdominal surgery. These 2 studies were of similar design; however, they differed in terms of study hypothesis, efficacy analyses, and geographic location.

In the 2 studies, patients were randomized to receive a 40-mg dose of aprepitant, a 125-mg dose of aprepitant, or 4 mg of IV ondansetron as a single dose. The study drug 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 125-mg dose did not demonstrate any additional clinical benefit over the 40-mg dose and is not a recommended dosage regimen.

Table 3. Study Design

	Design	*Surgery Type*	*Treatment Arms*	*Primary Endpoint(s)*	*Secondary Endpoint(s)*	*Additional Endpoint(s)*
Study 1	Multinational, randomized, double-blind trial (N = 892)	Open abdominal (general anesthesia)	Oral Aprepitant 40 mg Oral Aprepitant 125 mg IV Ondansetron 4 mg	• Complete response 0 to 24 hours (noninferiority) • No vomiting 0 to 24 hours	• No vomiting 0 to 48 hrs	• Peak nausea score • Time to first emesis • Time to first rescue therapy
Study 2	United States randomized, double-blind trial (N = 766)	Open abdominal (general anesthesia)	Oral Aprepitant 40 mg Oral Aprepitant 125 mg IV Ondansetron 4 mg	• Complete response 0 to 24 hours	• No vomiting 0 to 24 hours • No vomiting 0 to 48 hours • No rescue therapy 0 to 24 hours	• Peak nausea score 0 to 24 hours

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

Phase 3 Clinical Trials (CONT)

Of the 564 patients who received 40 mg aprepitant, 92% were women and 8% were men; of these, 58% were white, 13% Hispanic American, 7% multiracial, 14% black, 6% Asian, and 2% other. The age of patients treated with 40 mg aprepitant ranged from 19 to 84 years, with a mean age of 46.1 years. Forty-six patients were 65 years or older, with 13 patients being 75 years or older. The antiemetic activity of aprepitant was evaluated during the 0- to 48-hour period following the end of surgery.[1]

Complete response was defined as no vomiting and no use of rescue therapy.

Study 1[1,2]

Study 1 included 2 co-primary endpoints: complete response, and no vomiting through the first 24 hours. The complete response endpoint was tested for noninferiority before testing it for superiority. The secondary endpoint was the proportion of patients experiencing no vomiting through 48 hours after surgery compared to IV ondansetron.

Aprepitant demonstrated superiority to IV ondansetron in the co-primary endpoints of complete response in the first 24 hours following surgery and no vomiting through 24 hours. In the secondary endpoint of no vomiting through 48 hours, aprepitant demonstrated superiority to IV ondansetron.

Study 2[1,3]

The primary efficacy endpoint of Study 2 was the proportion of patients experiencing complete response (no vomiting and no use of rescue therapy through the first 24 hours after surgery compared to IV ondansetron), with the secondary endpoints being the proportion of patients experiencing no vomiting through the first 24 and 48 hours after surgery compared to IV ondansetron, and the proportion of patients who did not need rescue medication in the first 24 hours compared to IV ondansetron.

While Study 2 failed to satisfy its primary hypothesis that the study drug was superior to IV ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery, aprepitant was shown to have a clinically meaningful effect with respect to the 2 secondary endpoints, no vomiting during the first 24 and 48 hours after surgery, and was associated with 16% and 17% improvements over IV ondansetron, respectively.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

Clinically Significant CYP3A4 Drug Interactions: Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Use of pimozide, a CYP3A4 substrate, with APONVIE is contraindicated. Use of APONVIE with strong CYP3A4 inhibitors (eg, ketoconazole) may increase plasma concentrations of aprepitant and result in an increased risk of adverse reactions related to APONVIE. Use of APONVIE with strong CYP3A4 inducers (eg, rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of APONVIE.

Phase 3 Clinical Trials (CONT)

Complete Response Endpoint[1-3]

Figure 6. Study 1 Co-Primary Endpoint: Complete Response

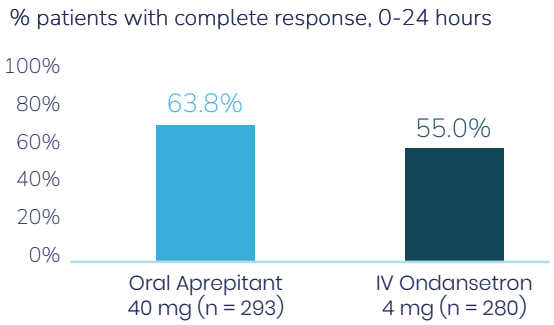
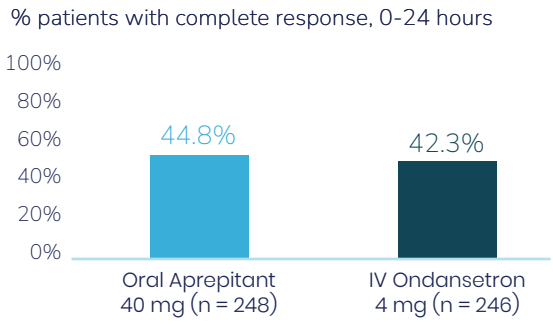


Figure 7. Study 2 Primary Endpoint: Complete Response



The above graphs show the percentage of study participants who experienced complete response (no vomiting and no use of rescue therapy) through the first 24 hours after surgery compared to IV ondansetron in both studies. Oral aprepitant is shown in light blue, and IV ondansetron is shown in dark teal.

In Study 1, aprepitant demonstrated superiority to IV ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following the end of surgery (1-tail 97.5% CI of OR: LB = 1.02[a]).

In Study 2, aprepitant failed to demonstrate superiority to IV ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery ($P = .61$).

Complete response: no vomiting and no use of rescue therapy.
[a]OR: estimated odds ratio for aprepitant versus IV ondansetron. A value of >1 favors aprepitant over IV ondansetron. LB: lower bound. Superiority: if LB > 1.

APONVIE has demonstrated bioequivalence to oral aprepitant in a clinical trial.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

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. Monitor the INR in patients on chronic warfarin therapy in the 2-week period particularly at 7 to 10 days, following administration of APONVIE.

Phase 3 Clinical Trials (CONT)

Superior Vomiting Prevention Through 24 Hours[1-3]

Figure 8. Study 1 Co-Primary Endpoint: No Vomiting 0-24 Hours

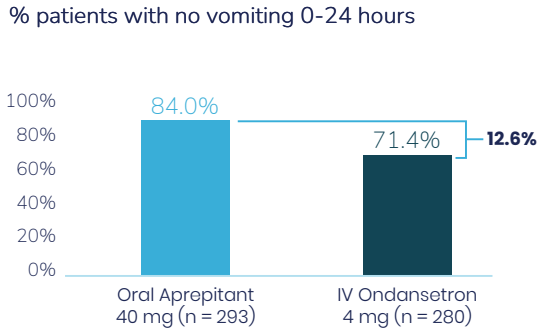
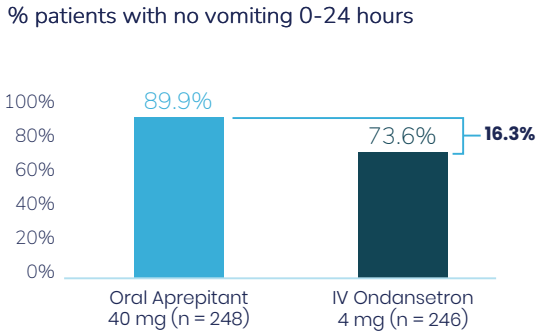


Figure 9. Study 2 Secondary Endpoint: No Vomiting 0-24 Hours



In both studies, oral aprepitant had a clinically meaningful effect with respect to the endpoint of no vomiting in the first 24 hours after surgery compared to IV ondansetron.

In Study 1, aprepitant demonstrated superiority to IV ondansetron in the co-primary endpoint of no vomiting in the 24 hours following the end of surgery ($P < .001$[a]).

In Study 2, aprepitant demonstrated superiority to IV ondansetron in the prevention of PONV as measured by the proportion of patients with no vomiting in the 24 hours following the end of surgery ($P < .001$[b]).

[a]*P* value of 2-tail test at the .05 significance level.
[b]Unadjusted *P* value.

APONVIE has demonstrated bioequivalence to oral aprepitant in a clinical trial.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

Risk of Reduced Efficacy of Hormonal Contraceptives: The efficacy of hormonal contraceptives may be reduced for 28 days following administration of APONVIE. Advise patients to use effective alternative or back-up methods of non-hormonal contraception for 1 month following administration of APONVIE.

Phase 3 Clinical Trials (CONT)

Superior Vomiting Prevention Through 48 Hours[1-3]

Figure 10. Study 1 Secondary Endpoint: No Vomiting 0-48 Hours

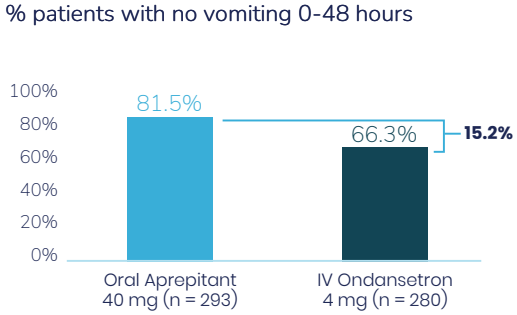
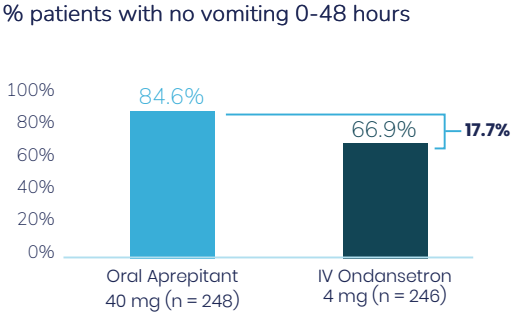


Figure 11. Study 2 Secondary Endpoint: No Vomiting 0-48 Hours



In Study 1, in addition to showing superiority to IV ondansetron for no vomiting through 48 hours ($P < .001$[a]), aprepitant also delayed time to first vomiting when compared to IV ondansetron. **Half as many patients vomited when treated with oral aprepitant** compared to IV ondansetron.

In Study 2, aprepitant showed an improvement over IV ondansetron through 48 hours ($P < .001$[b]). In an analysis adjusting for rescue therapy, patients receiving oral aprepitant **experienced 75% fewer episodes of vomiting**, on average, compared to those taking IV ondansetron.

Aprepitant significantly reduced vomiting, with a reduction of greater than 40% in the proportion of patients vomiting after surgery compared to ondansetron. The greatest differences were observed 24 to 48 hours after surgery, when patients are frequently home without access to effective treatment.

[a]*P* value of 2-tail test at the .05 significance level.
[b]Unadjusted *P* value.

APONVIE has demonstrated bioequivalence to oral aprepitant in a clinical trial.

IMPORTANT SAFETY INFORMATION

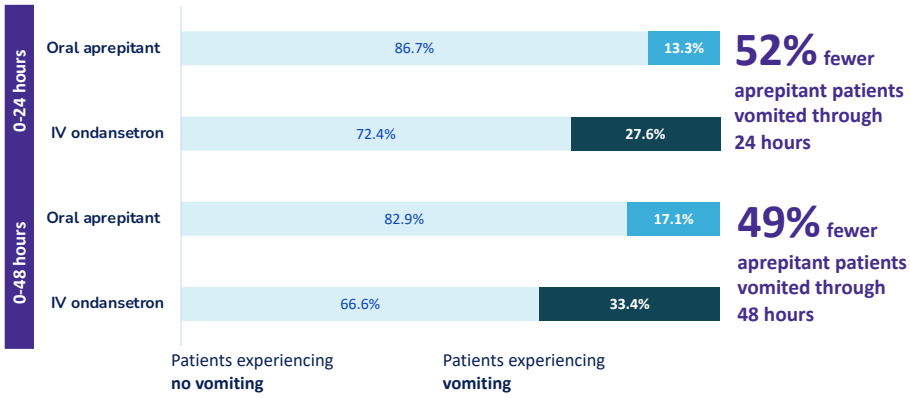
Use in Specific Populations

Avoid use of APONVIE in pregnant women as alcohol is an inactive ingredient in APONVIE. There is no safe level of alcohol exposure in pregnancy.

Phase 3 Clinical Trials (CONT)

Approximately 50% Fewer Patients Vomited in the First 24 and 48 Hours After Receiving Aprepitant[1-3]

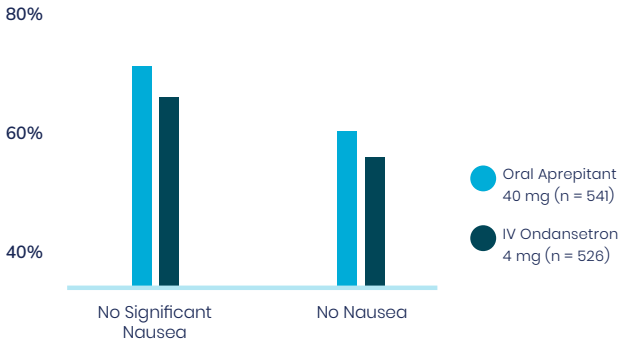
Pooled Analysis of Phase 3 Clinical Studies[a]



Nausea: Aprepitant Versus IV Ondansetron[22]

This post hoc analysis of pooled data from the 2 randomized, active-controlled clinical trials of oral aprepitant supporting the approval of APONVIE in the United States was performed to further explore the potential efficacy profile of aprepitant versus IV ondansetron in terms of nausea and use of rescue therapy in the first 24 hours following surgery.

Figure 12. Pooled analysis: % without single/composite events, 0-24 hours



Among patients who did not require rescue medication, more patients who took aprepitant experienced no nausea compared to those who had taken IV ondansetron, suggesting that nausea may be reduced more by aprepitant than by IV ondansetron.

[a]Descriptive statistics pooled across 2 randomized, double-blind trials of oral aprepitant 40 mg (0-24 hours: n = 541, 0-48 hours: n = 539) versus active-control ondansetron IV 4 mg (0-24 hours: n = 526, 0-48 hours: n = 525) for the prevention of PONV following open abdominal surgery under general anesthesia.

Note: Nausea was rated on a verbal rating scale of 0 to 10, with a score of 0 meaning no nausea and a score of 10 meaning the worst nausea ever. "No significant nausea" was defined as a peak VRS score ≤4 in the first 24 hours. Rescue therapy was available if the patient requested it, if the patient had > 1 episode of vomiting or retching, or if the patient had nausea lasting longer than 15 minutes. When increasing statistical power with this combined sample, nominal $P < .035$ for each comparison in favor of aprepitant 40 mg—warranting a further, prospective study. (Two-tail P of the odds ratio vs IV ondansetron 4 mg IV for each exploratory endpoint.)

IMPORTANT SAFETY INFORMATION

Adverse Reactions

Most common adverse reactions (incidence ≥3%) for APONVIE are constipation, fatigue, and headache and for oral aprepitant are constipation and hypotension.

Report side effects to Heron at 1-844-437-6611 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

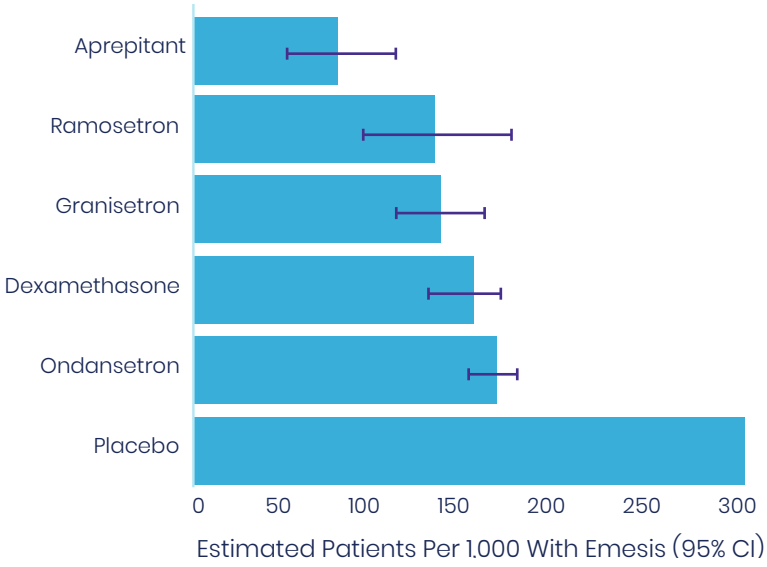
Cochrane Meta-analysis[23]

Cochrane Meta-Analysis: Aprepitant Is the Most Efficacious Compound for the Prevention of Vomiting After Surgery With High-Confidence Evidence

In an independent 2020 Cochrane meta-analysis of 585 studies and 97,516 patients, aprepitant was ranked as the most effective single agent with a high certainty of evidence among drugs with a PONV prophylactic indication, with the lowest rate of vomiting.

Approximately 100 fewer patients vomited per 1,000 compared with patients treated with ondansetron, as seen in Figure 13.

Figure 13. Ranking of most effective single-agent prophylactics with high-confidence evidence vs placebo through 24 hours



Aprepitant Is Part of the Top-Performing Multimodal Approaches for the Prevention of Vomiting After Surgery

Aprepitant-containing multimodal regimens were the most effective combinations. The most effective combination contained aprepitant, and aprepitant was included in 2 of the top 3 most effective combinations.

Table 4. Top 3 most effective combinations

Of 36 combination regimens analyzed in this Cochrane review (and 65 overall regimens), the top 3 most effective combinations versus placebo were:

1. **Aprepitant / Palonosetron**
2. **Dexamethasone / Metoclopramide / Ondansetron**
3. **Aprepitant / Ramosetron**

IMPORTANT SAFETY INFORMATION

Contraindications

APONVIE is contraindicated in patients with a history of hypersensitivity to aprepitant or any component of the product, and in patients taking pimozide. Increased pimozide levels may cause serious or life-threatening reactions, such as QT prolongation.

Guidelines and clinical evidence support the use of APONVIE as part of a multimodal approach for those at moderate-to-high risk of developing PONV

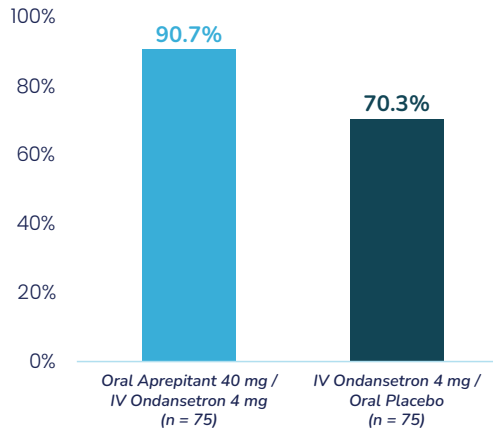
According to the newest version of the Society for Ambulatory Anesthesiology's consensus guidelines on the management of PONV, **multimodal prophylaxis should be considered for patients with one or more risk factors.**[7]

As an **NK_1 antagonist (a guideline-recommended class of PONV medications),** APONVIE has little or no affinity for serotonin (5-HT3), dopamine, and corticosteroid receptors, the targets of other therapies for PONV, which makes it a **good option for use as a first-line therapy in a multimodal approach for patients at moderate-to-high risk.**[1,7]

Vallejo et al: Prospective Study Shows Aprepitant as Part of a Multimodal Approach Is Highly Effective for Moderate-to-High-Risk Plastic Surgery Patients[24]

This prospective, double-blinded, randomized 2-arm study evaluated the occurrence of vomiting and the severity of nausea in the 48 hours following surgery in 150 ambulatory plastic surgery patients undergoing general anesthesia with 2 or more risk factors for PONV. Patients received either aprepitant plus IV ondansetron or IV ondansetron and placebo.

Figure 14. Primary endpoint: percent of patients with no vomiting in the first 48 hours following surgery



When aprepitant was added to IV ondansetron, 20% more patients experienced no vomiting in the first 48 hours following surgery (*P* = .003). All episodes of vomiting occurred in the first 12 hours.

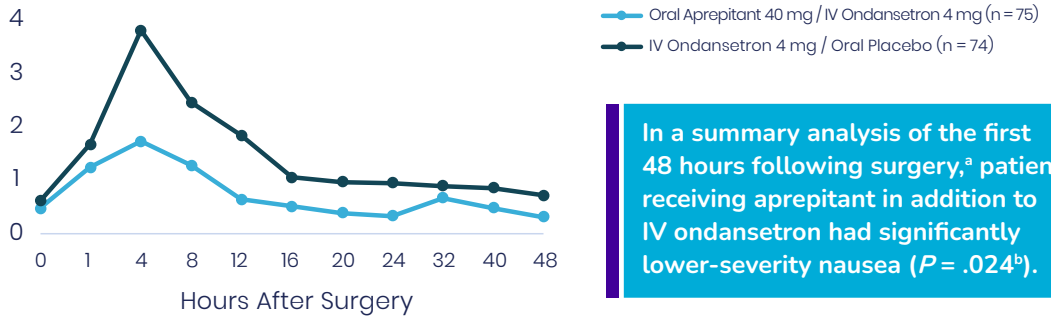
IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

APONVIE as Part of a Multimodal Regimen for PONV Prophylaxis (CONT)

Figure 15. Secondary endpoint: mean nausea verbal rating score in the first 48 hours following surgery[24]



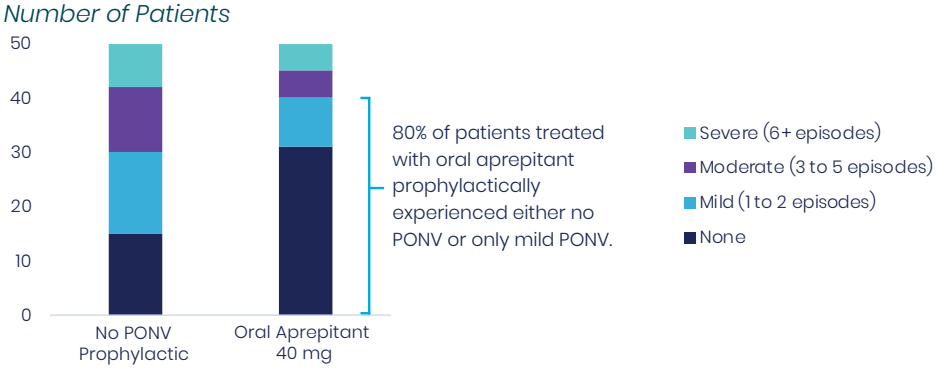
In a summary analysis of the first 48 hours following surgery,[a] patients receiving aprepitant in addition to IV ondansetron had significantly lower-severity nausea (*P* = .024[b]).

Note: Nausea was rated on a verbal rating scale of 0 to 10, with a score of 0 meaning no nausea and a score of 10 meaning the worst nausea ever.
[a]Mean differences in VRS scores over 48 hours tested simultaneously with a multivariate analysis of variance.
[b]Unadjusted *P* value.

Dilorio et al: Retrospective Chart Review Showed That Total Hip Arthroplasty and Total Knee Arthroplasty Patients Receiving Aprepitant Experienced Reduced Severity of PONV[25]

Fifty patients undergoing total hip arthroplasty or total knee arthroplasty who received a preoperative dose of oral aprepitant were matched to 50 patients who received no PONV prophylactic. Patients in both groups were treated postoperatively with IV ondansetron 4 mg only as rescue medication if PONV occurred. Patients' charts were retrospectively reviewed. Instances of PONV were noted for the entire length of hospital stay. **On average, patients receiving oral aprepitant had approximately 40% fewer episodes of PONV, required less than half the amount of rescue medication, and were ready for discharge a day sooner.**

Figure 16. Severity of PONV



IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

Clinically Significant CYP3A4 Drug Interactions: Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Use of pimozide, a CYP3A4 substrate, with APONVIE is contraindicated. Use of APONVIE with strong CYP3A4 inhibitors (eg, ketoconazole) may increase plasma concentrations of aprepitant and result in an increased risk of adverse reactions related to APONVIE. Use of APONVIE with strong CYP3A4 inducers (eg, rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of APONVIE .

APONVIE as Part of a Multimodal Regimen for PONV Prophylaxis (CONT)

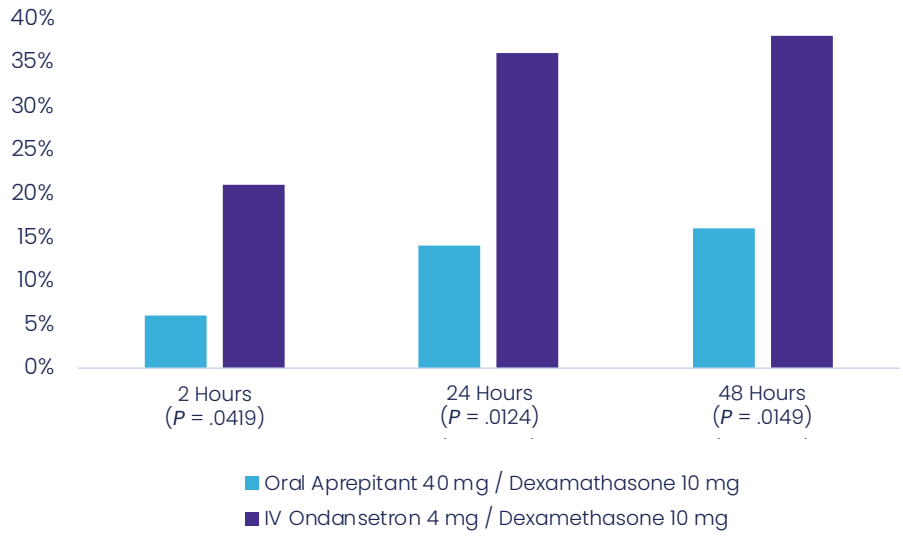
Table 5. Episodes of PONV, doses of antiemetics, and length of stay[25]

	No PONV Prophylactic (n = 50)	*Oral Aprepitant 40 mg (n = 50)*
Average episodes of PONV	2.7	1.6
Average number of times antiemetics were administered as rescue (range)	1.25 (0 to 5)	0.61 (0 to 4)
Average length of stay (days)	3.31	2.31

Habib et al: Prospective Study Showed That Aprepitant Reduced the Incidence of Vomiting in Craniotomy Patients[26]

In this prospective, double-blind, randomized study of 104 patients undergoing craniotomy under general anesthesia, patients received dexamethasone as well as either oral aprepitant or IV ondansetron. Though the complete response was similar between treatment groups, **using aprepitant in addition to dexamethasone significantly reduced the incidence of vomiting compared to IV ondansetron at multiple timepoints.**

Figure 17. Incidence of Vomiting



Complete response: no vomiting and no use of rescue therapy.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

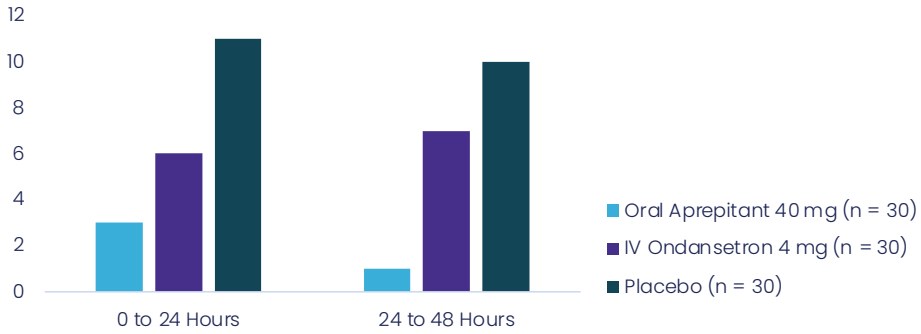
Decrease in INR with Concomitant Warfarin: Use of aprepitant with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the International Normalized Ratio (INR) of prothrombin time. Monitor the INR in patients on chronic warfarin therapy in the 2-week period particularly at 7 to 10 days, following administration of APONVIE.

APONVIE as Part of a Multimodal Regimen for PONV Prophylaxis (CONT)

Kaur et al: Prospective Study Showed Aprepitant Demonstrated a Longer-Acting Effect than IV Ondansetron in Laparoscopic Cholecystectomy Patients[27]

In a randomized, double-blind, prospective trial, 90 patients undergoing laparoscopic cholecystectomy were treated with either oral aprepitant 40 mg, IV ondansetron 4 mg, or placebo. Though nausea scores across both treatment groups were similar, and the difference in the number of episodes of vomiting was not statistically significant in the first 24 hours, fewer episodes of vomiting were reported in the 24- to 48-hour time period in patients treated with aprepitant than in those treated with IV ondansetron. **There was no statistically significant difference in early episodes of vomiting between the aprepitant and IV ondansetron groups; however, aprepitant demonstrated a longer-acting effect than IV ondansetron, and better prevented delayed vomiting.**

Figure 18. Episodes of Vomiting



Additional Clinical Data of Aprepitant

Trimas et al: Retrospective Analysis Shows Aprepitant Reduced Postoperative Nausea in Facial Plastic Surgery[28]

In a retrospective analysis of 172 consecutive patients undergoing facial plastic surgery with general anesthesia, patients were treated with IV ondansetron and dexamethasone. In addition, 56 patients also received aprepitant. **The addition of aprepitant reduced the likelihood of postoperative nausea compared to IV ondansetron and dexamethasone, with 98% of patients receiving aprepitant experiencing no PONV, compared to 84% of patients receiving IV ondansetron and dexamethasone.**

Hartrick et al: Open-Label Study Showed That Aprepitant Outperformed Multimodal PONV Therapies in Total Knee Arthroplasty[29]

In a sequential, open-label, matched case control study, 24 patients underwent total knee arthroplasty with extended-release epidural morphine. One group of patients received ondansetron and dexamethasone, combined with either metoclopramide, diphenhydramine, or prochlorperazine. The other group received only oral aprepitant preoperatively. Incidence of PONV was then compared between the two groups. In this study, patients were considered positive for PONV if they reported any incidence of nausea or vomiting. **Aprepitant used as a single agent significantly reduced the incidence of PONV compared to a multimodal antiemetic regimen, with 75% of patients who received aprepitant experiencing no PONV, compared to 25% of patients who received the multimodal therapy (*P* = .039).**

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont)

Risk of Reduced Efficacy of Hormonal Contraceptives: The efficacy of hormonal contraceptives may be reduced for 28 days following administration of APONVIE. Advise patients to use effective alternative or back-up methods of non-hormonal contraception for 1 month following administration of APONVIE.

CLINICAL SAFETY

Adverse Reactions

In 2 studies of more than 560 patients undergoing general anesthesia, there were no significant differences in the incidence of adverse events between oral aprepitant and IV ondansetron[1-3]

Table 6. Pooled Analysis: Adverse Reactions[1,a]

	Oral Aprepitant 40 mg (n = 564)	*IV Ondansetron 4 mg (n = 538)*
Constipation	9%	8%
Hypotension	6%	5%

Aprepitant, the active ingredient in APONVIE, has been used for PONV since 2006.[5] Aprepitant is well tolerated, with an established safety profile. IV aprepitant has been administered, even at a higher dose (130 mg), in more than 2.5 million doses to treat chemotherapy-induced nausea and vomiting.[6]

Aprepitant is not associated with QT prolongation, urinary retention, blurred vision, cognitive issues including sedation, or instances of serotonin syndrome.[1]

The most common adverse reactions (incidence ≥3%, and greater than IV ondansetron) in patients treated with aprepitant were mild to moderate, and included constipation (9%, compared to 8% with IV ondansetron) and hypotension (6%, compared to 5% with IV ondansetron).[1]

In addition, 2 serious adverse reactions were reported in PONV clinical studies in patients taking a higher than recommended dose of oral aprepitant: 1 case of constipation, and 1 case of subileus.[1]

Upon administration of aprepitant, the efficacy of hormonal contraceptives may be reduced. Patients using hormonal contraceptives should be advised to use an alternative nonhormonal contraceptive (such as condoms and spermicides) during treatment with APONVIE and for 1 month following the last dose.[1]

Aprepitant is contraindicated for use with pimozide. In patients on chronic warfarin therapy, monitor the prothrombin time following administration of aprepitant. Avoid concomitant use of moderate-to-strong CYP3A4 inhibitors and strong CYP3A4 inducers.[1]

[a]Events included adverse reactions with an incidence ≥3% and at a greater incidence than IV ondansetron.

CONCLUSIONS

Postoperative nausea and vomiting is a common adverse effect of anesthesia, surgery, and postoperative opioid use, with an estimated incidence of 30% in the general surgical population and up to 80% in high-risk patients.[7] Ondansetron, one of the most commonly used antiemetics, has a relatively short half-life (3 to 6 hours).[8] Even when treated with ondansetron or other antiemetics, more than 30% of patients still experience postoperative nausea and vomiting.[2] Poorly managed PONV affects overall length of hospital stay and is also a major cause of patient dissatisfaction after surgery, with patients ranking vomiting as the most undesirable outcome when asked about postsurgical complications.[9–12]

As the first and only IV NK_1 antagonist for the prevention of PONV, APONVIE crosses the blood-brain barrier and binds to NK_1 receptors with high affinity, blocking substance P, which is found in areas thought to be involved in the vomiting reflex.[1,3] As an NK_1 antagonist (a guideline-recommended class of PONV medications) APONVIE has little or no affinity for serotonin, dopamine, and corticosteroid receptors (the targets of other PONV therapies), which makes it a good option for use as a first-line therapy in a multimodal approach for patients at **moderate-to-high risk.**[1,7]

APONVIE has demonstrated bioequivalence to oral aprepitant 40 mg in a Phase 1 clinical study, showing that APONVIE behaves predictably in the human body. As expected, due to IV administration, plasma concentrations of aprepitant were higher following administration of APONVIE compared with oral aprepitant for approximately 3 hours. By the 4-hour timepoint, the plasma concentrations for the 2 formulations converged and remained similar.[4] IV administration allows the drug to enter directly into systemic circulation without the delay associated with absorption processes. This results in 100% bioavailability, making it the best way to deliver a drug rapidly and accurately, and bypassing first-pass metabolism.[21]

In Phase 3 clinical trials, aprepitant (the active ingredient in APONVIE) demonstrated effective vomiting prevention versus standard-of-care IV ondansetron through both 24 and 48 hours.[1-3] In Study 1, **half as many patients vomited when treated with oral aprepitant** compared to IV ondansetron.[2] In Study 2, in an analysis adjusting for rescue therapy, patients receiving oral aprepitant **experienced 75% fewer episodes of vomiting**, on average, compared to those receiving IV ondansetron.[3]

Aprepitant significantly reduced vomiting, with a reduction of greater than 40% in the proportion of patients vomiting after surgery compared to IV ondansetron. The greatest differences were observed 24 to 48 hours after surgery, when patients are frequently home without access to effective treatment.[1-3]

IMPORTANT SAFETY INFORMATION

Use in Specific Populations

Avoid use of APONVIE in pregnant women as alcohol is an inactive ingredient in APONVIE. There is no safe level of alcohol exposure in pregnancy.

CONCLUSIONS (CONT)

While aprepitant has been shown to be the most effective single agent with a high certainty of evidence for the prevention of PONV, guidelines and clinical evidence also support its use as part of a multimodal approach.[7,23-29]

In an independent 2020 Cochrane meta-analysis of 585 studies and 97,516 patients, aprepitant was ranked as the most effective single agent with a high certainty of evidence among drugs with a PONV prophylactic indication, with the lowest rate of vomiting. Aprepitant was also part of the top-performing multimodal approaches for the prevention of vomiting after surgery. The most effective ranked combination contained aprepitant, and aprepitant was included in 2 of the 3 most effective combinations.[23]

Aprepitant has been used for PONV since 2006.[5] In 2 studies of more than 560 patients undergoing general anesthesia, there were no significant differences in the incidence of adverse events between aprepitant and IV ondansetron.[1-3] Aprepitant is not associated with QT prolongation, urinary retention, blurred vision, cognitive issues including sedation, or instances of serotonin syndrome.[1]

Aprepitant is well tolerated, with an established safety profile. IV aprepitant has been administered, even at a higher dose (130 mg), in more than 2.5 million doses to treat chemotherapy-induced nausea and vomiting.[6]

Reducing PONV can enable providers to increase patient satisfaction, improve patient outcomes, and avoid complications; reduce PACU time, LOS, readmissions, and costs; and avoid operational challenges and burdens related to addressing PONV.[7,9-13,30,31]

ABBREVIATIONS

AUC_{0-24h}: area under the concentration-time curve from 0 to 24 hours postdose.

AUC_{inf}: area under the concentration-time curve extrapolated to infinity.

AUC_{last}: area under the concentration-time curve to the time of the last quantifiable concentration.

C_{max}: maximum concentration.

PACU: post-anesthesia care unit.

LOS: length of stay.

T_{max}: time of occurrence of maximum concentration.

IMPORTANT SAFETY INFORMATION

Adverse Reactions

Most common adverse reactions (incidence ≥3%) for APONVIE are constipation, fatigue, and headache and for oral aprepitant are constipation and hypotension.

Report side effects to Heron at 1-844-437-6611 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

APONVIE™
(aprepitant) injectable emulsion

Indication

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.

IMPORTANT SAFETY INFORMATION

Contraindications

APONVIE is contraindicated in patients with a history of hypersensitivity to aprepitant or any component of the product, and in patients taking pimozide. Increased pimozide levels may cause serious or life-threatening reactions, such as QT prolongation.

Warnings and Precautions

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

Clinically Significant CYP3A4 Drug Interactions: Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Use of pimozide, a CYP3A4 substrate, with APONVIE is contraindicated. Use of APONVIE with strong CYP3A4 inhibitors (eg, ketoconazole) may increase plasma concentrations of aprepitant and result in an increased risk of adverse reactions related to APONVIE. Use of APONVIE with strong CYP3A4 inducers (eg, rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of APONVIE.

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. Monitor the INR in patients on chronic warfarin therapy in the 2-week period particularly at 7 to 10 days, following administration of APONVIE.

Risk of Reduced Efficacy of Hormonal Contraceptives: The efficacy of hormonal contraceptives may be reduced for 28 days following administration of APONVIE. Advise patients to use effective alternative or back-up methods of non-hormonal contraception for 1 month following administration of APONVIE.

Use in Specific Populations

Avoid use of APONVIE in pregnant women as alcohol is an inactive ingredient in APONVIE. There is no safe level of alcohol exposure in pregnancy.

Adverse Reactions

Most common adverse reactions (incidence ≥3%) for APONVIE are constipation, fatigue, and headache and for oral aprepitant are constipation and hypotension.

Report side effects to Heron at 1-844-437-6611 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information.

APONVIE™
(aprepitant) injectable emulsion

REFERENCES

1. APONVIE [package insert]. San Diego, CA: Heron Therapeutics Inc; 2022.
2. Diemunsch P, Gan TJ, Philip BK, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind Phase III trial in patients undergoing open abdominal surgery. *Brit J Anaesth*. 2007;99(2):202-211. doi:10.1093/bja/aem133.
3. Gan TJ, Apfel CC, Kovac A, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. *Anesth Analg*. 2007;104(5):1082-1089. doi:10.1213/01.ane.0000263277.35140.a3.
4. Data on file. Study HTX-019-111. San Diego, CA: Heron Therapeutics Inc; 2021.
5. Korvick J; Center for Drug Evaluation and Research. Supplemental NDA approval letter: NDA 21-549/S-010 (Emend). Rockville, MD: US Food and Drug Administration; June 30, 2006. https://www.accessdata.fda.gov/drugsatfda_ docs/appletter/2006/021549s010LTR.pdf. Accessed March 14, 2022.
6. Data on file. CINVANTI quantity sold data. San Diego, CA: Heron Therapeutics Inc; 2021.
7. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2020;131(2):411-448. doi:10.1213/ane.0000000000004833.
8. Zofran [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017.
9. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg*. 1999;89(3):652-658. doi:10.1097/00000539-199909000-00022.
10. Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol or placebo. *Anesthesiology*. 2000;92(4):958-967. doi.10.1097/00000542-200004000-00012.
11. Habib AS, Chen Y-T, Taguchi A, Hu XH, Gan TJ. Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis. *Curr Med Res Opin*. 2006;22(6):1093-1099. doi:10.1185/030079906X104830.
12. Golembiewski J, Chernin E, Chopra T. Prevention and treatment of postoperative nausea and vomiting. *Am J Health Syst Pharm*. 2005;62(12):1247-1260. doi:10.1093/ajhp/62.12.1247.
13. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention. *Anesthesiology*. 1992;77(1):162-184. doi:10.1097/00000542-199207000-00023.
14. Chiu C, Aleshi P, Esserman LJ, et al. Improved analgesia and reduced post-operative nausea and vomiting after implementation of an enhanced recovery after surgery (ERAS) pathway for total mastectomy. *BMC Anesthesiol*. 2018;18(1):41. doi:10.1186/s12871-018-0505-9.
15. Kadota T, Kakuta N, Horikawa YT, et al. Plasma substance P concentrations in patients undergoing general anesthesia: an objective marker associated with postoperative nausea and vomiting. *JA Clin Rep*. 2016;2(1):9. doi:10.1186/s40981-016-0034-9.
16. Gan TJ. Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist-based pharmacotherapy. *CNS Drugs*. 2007;21(10):813-833. doi:10.2165/00023210-200721100-00003.
17. Le TP, Gan TJ. Update on the management of postoperative nausea and vomiting and postdischarge nausea and vomiting in ambulatory surgery. *Anesthesiol Clin*. 2010;28(2):225-249. doi:10.1016/j.anclin.2010.02.003.
18. Data on file. Summary of clinical pharmacology studies. San Diego, CA: Heron Therapeutics Inc. 2021.
19. Van Laere K, De Hoon J, Bormans G, et al. Equivalent dynamic human brain NK1- receptor occupancy following single-dose i.v. fosaprepitant vs. oral aprepitant as assessed by PET imaging. *Clin Pharmacol Ther*. 2012;92(2):243-250. doi:10.1038/clpt.2012.62.
20. EMEND [package insert]. Whitehouse Station, NJ: Merck & Co Inc: 2019.
21. Ruiz, ME, Scioli Montoto, S. Routes of drug administration. In: Talevi A, Quiroga P, eds. *ADME Processes in Pharmaceutical Sciences*. Springer, Cham. Published December 1, 2018. doi:10.1007/978-3-319-99593-9_6.
22. Diemunsch P, Apfel C, Gan TJ, et al. Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. *Curr Med Res Opin*. 2007;23(10):2559-2565. doi:10.1185/030079907X233115.
23. Weibel S, Schaefer MS, Raj D, et al. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: an abridged Cochrane network meta-analysis. *Anaesthesia*. 2021;76(7):962-973. doi:10.1111/anae.15295.
24. Vallejo MC, Phelps AL, Ibinson JW, et al. Aprepitant plus ondansetron compared with ondansetron alone in reducing postoperative nausea and vomiting in ambulatory patients undergoing plastic surgery. *Plast Reconstr Surg*. 2012;129(2):519- 526. doi:10.1097/PRS.0b013e31822b6932.
25. Dilorio TM, Sharkey PF, Hewitt AM, Parvizi J. Antiemesis after total joint arthroplasty: does a single preoperative dose of aprepitant reduce nausea and vomiting? *Clin Orthop Relat Res*. 2010;468(9):2405-2409. doi:10.1007/s11999-010-1357-x.
26. Habib AS, Keifer JC, Borel CO, White WD, Gan TJ. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. *Anesth Analg*. 2011;112(4):813-818. doi:10.1213/ANE.0b013e3181ff47e2.
27. Kaur U, Sharma VK, Sidhu JS. A comparison of aprepitant and ondansetron in prophylaxis of postoperative nausea and vomiting in laparoscopic cholecystectomy. *Sch J App Med Sci*. 2014;2(3B):1020-1027.
28. Trimas SJ, Trimas MD. Use of aprepitant and factors associated with incidence of postoperative nausea and vomiting in patients undergoing facial plastic surgery. *JAMA Facial Plast Surg*. 2015;17(4):251-255. doi:10.1001/ jamafacial.2015.0307.
29. Hartrick CT, Tang YS, Hunstad D, et al. Aprepitant vs. multimodal prophylaxis in the prevention of nausea and vomiting following extended-release epidural morphine. Pain Pract. 2010;10(3):245-248. doi:10.1111/j.1533-2500.2010.00364.x. *JAMA Facial Plast Surg*. 2015;17(4):251-255. doi:10.1001/ jamafacial.2015.0307.
30. Fortier J, Chung F, Su J. Unanticipated admission after ambulatory surgery—a prospective study. *Can J Anaesth*. 1998;45(7):612-619. doi:10.1007/BF03012088. vomiting following extended-release epidural morphine. Pain Pract. 2010;10(3):245-248. doi:10.1111/j.1533-2500.2010.00364.x.
31. Parra-Sanchez I, Abdallah R, You J, et al. A time-motion economic analysis of postoperative nausea and vomiting in ambulatory surgery. *Can J Anaesth*. 2012;59(4):366-375. doi:10.1007/s12630-011-9660-x.

APONVIE™

(aprepitant) injectable emulsion

HERON THERAPEUTICS®

4242 CAMPUS POINT COURT, SUITE 200 • SAN DIEGO, CA 92121 • 858-251-4400