APONVIE™
(aprepitant) injectable emulsion

ONE PUSH TO PREVENT PONV

First and only IV NK_1 antagonist for prevention of PONV[1]

Superior vomiting prevention versus ondansetron through 48 hours[1-3,a]

Single IV push[1]

Comparable safety profile to IV ondansetron without QT prolongation[1]

Reaches therapeutic plasma concentrations associated with ≥97% receptor occupancy within 5 minutes[1,4,5,b]

[a]Unadjusted *P* value.
[b]The relationship between receptor occupancy and efficacy has not been established.

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.

Please see Important Safety Information throughout and accompanying full Prescribing Information.

THE PREVALENCE OF PONV

Postoperative nausea and vomiting are 2 of the most common adverse events following surgery, with an estimated incidence of 30% in the general surgical population and up to **80% in high-risk patients.**[6,7]

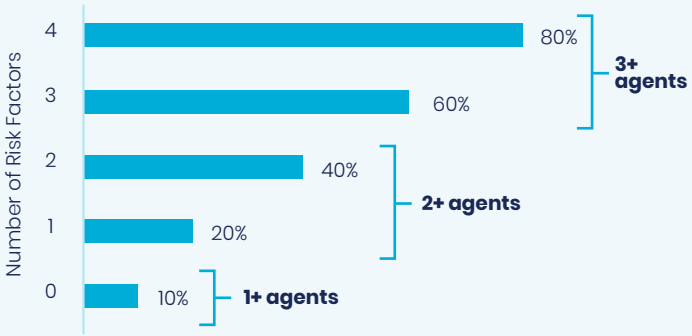
Ondansetron, one of the most commonly used antiemetics, has a relatively short half-life (3 to 6 hours). Even when treated with ondansetron or other antiemetics, **more than 30%** of patients still experience PONV within the first 48 hours after surgery—well after many outpatient surgery patients have been discharged and no longer have access to fast-onset IV antiemetics or direct care.[2,8]

APFEL SCORE[7]

A commonly used risk score for inpatients undergoing anesthesia is the simplified Apfel risk score, which is based on 4 predictors:

- Female sex
- Nonsmoking status
- History of PONV and/or motion sickness
- Use of postoperative opioids

APFEL SCORE:
Risk Level
Per # of Traits
0-1 Low Risk
2 Medium Risk
3+ High Risk



Incidence of PONV in Patients Undergoing General Anesthesia

PONV IS A SIGNIFICANT BURDEN TO PATIENTS AND FACILITIES

- 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 affects 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]

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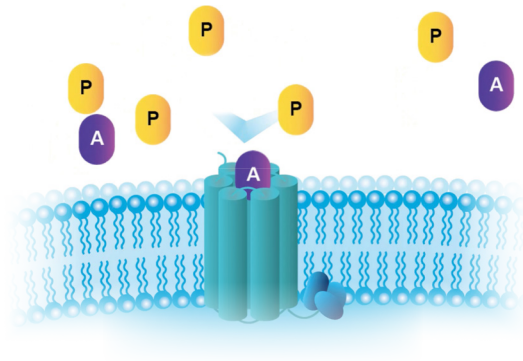
MECHANISM OF ACTION: APONVIE IS A NEUROKININ-1 (NK_1) ANTAGONIST

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.[3] Substance P binds to NK_1 receptors, inducing nausea or vomiting.[15]

APONVIE Blocks Substance P[1]

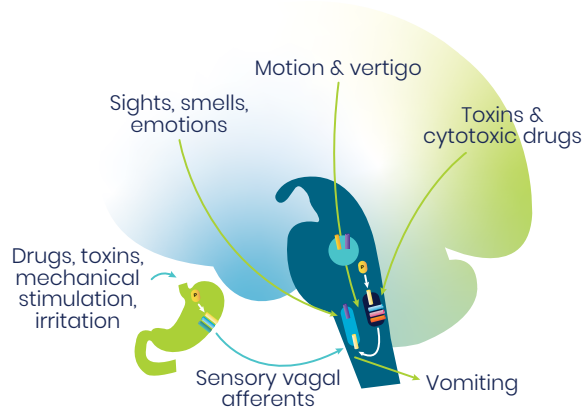


P Substance P
A APONVIE
NK_1 receptor
Cell membrane

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

APONVIE, as an NK_1 antagonist, binds to NK_1 receptors with high affinitiy, **blocking substance P** and preventing nausea and vomiting.[1]

The PONV Receptor Pathways[16,17]



VN
P Substance P
Vomiting Center
Chemoreceptor Trigger Zone
NK_1 Receptor
Muscainic Receptor
H_1 Receptor
$5HT_3$ Receptor
$5HT_4$ Receptor
D_2 Receptor

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

Warnings and Precautions

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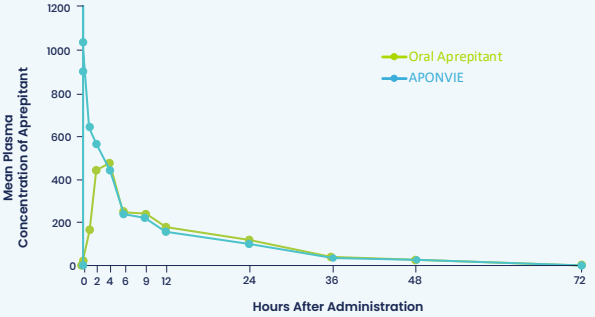
Clinically Significant CYP3A4 Drug Interactions: Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Use of pimozide, a CYP3A4 substrate, with APONVIE is contraindicated. Use of APONVIE with strong CYP3A4 inhibitors (eg, ketoconazole) may increase plasma 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 ONSET OF ACTION

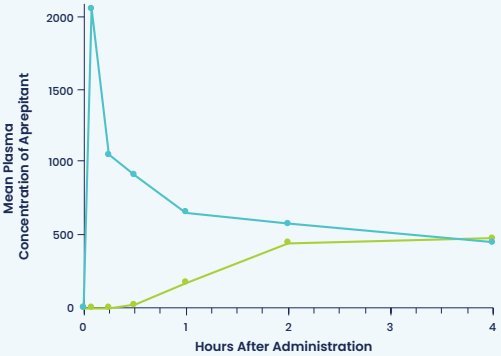
- APONVIE is delivered via a **single IV push.** Therapeutic plasma concentrations associated with **≥97% receptor occupancy in the brain are achieved within 5 minutes** for APONVIE—unlike oral aprepitant, which was taken 1 to 3 hours prior to induction of general anesthesia in clinical trials and does not reach maximum concentration until 3 hours after administration.[1,4,5,18,a]
- At 48 hours, therapeutic plasma concentrations associated with NK_1 receptor occupancy is estimated to be **maintained at >90%**[4,19,a]

Plasma Concentrations of APONVIE Versus Oral Aprepitant 0-72 Hours[19]



- **Plasma concentrations of aprepitant 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, staying similar from there on out.[19]
- 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.[20]

Plasma Concentrations of APONVIE Versus Oral Aprepitant 0-4 Hours[19]



[a]The relationship between receptor occupancy and efficacy has not been established.

APONVIE DEMONSTRATED BIOEQUIVALENCE TO ORAL APREPITANT[19]

Treatment	n[a]	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h·ng/mL)	AUC_{inf} (h·ng/mL)
APONVIE 32 mg IV injection	31	0.084 (0.083-0.105)	2,029 (21.4)	6,748 (30.3)	7,225 (28.4)
Oral aprepitant 40 mg	32	4.00 (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.
AUC_{0-24h}: area under the concentration-time curve from 0 to 24 hours post dose.
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.
T_{max}: time of occurrence of maximum concentration.

CLINICAL DATA FOR APREPITANT SHOWS SUPERIORITY OVER IV ONDANSETRON

Phase 3 Clinical Study Design[1-3]

Two Phase 3, multicenter, randomized, double-blind, active-controlled trials in patients receiving general anesthesia for open abdominal surgery were conducted to test the efficacy of NK_1 antagonist oral aprepitant versus standard-of-care IV ondansetron. Study 1 (N = 892) was multinational, while Study 2 (N = 766) took place in the United States.

Warnings and Precautions (CONT)

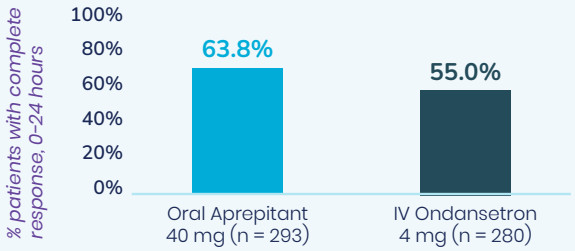
Decrease in INR with Concomitant Warfarin: Use of aprepitant with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the International Normalized Ratio (INR) of prothrombin time. Monitor the INR in patients on chronic warfarin therapy in the 2-week period particularly at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

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 Study Results: Oral Aprepitant Versus IV Ondansetron

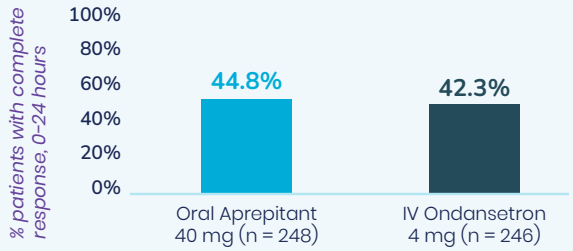
Complete Response: No Vomiting and No Use of Rescue Therapy

Study 1 Co-Primary Endpoint[1,2]



Aprepitant demonstrated superiority to IV ondansetron (1-tail 97.5% CI of OR: LB = 1.02[a]).

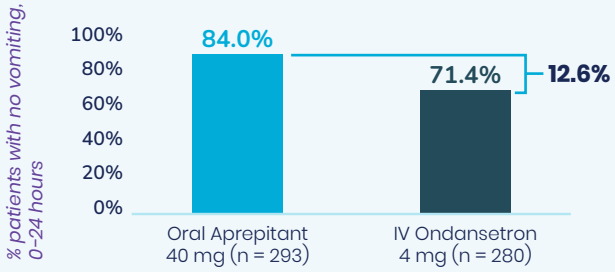
Study 2 Primary Endpoint[1,3]



Aprepitant did not demonstrate superiority to IV ondansetron ($P = .61$).

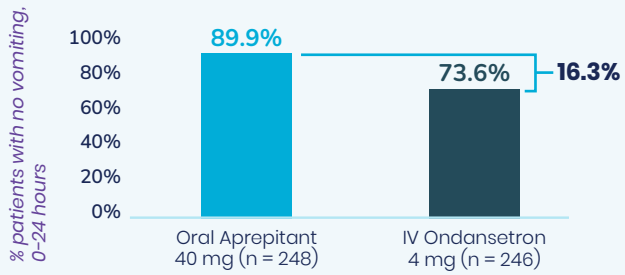
Superior Vomiting Prevention Through 24 Hours

Study 1 Co-Primary Endpoint[1,2]



Aprepitant demonstrated superiority to IV ondansetron ($P < .001$[b]).

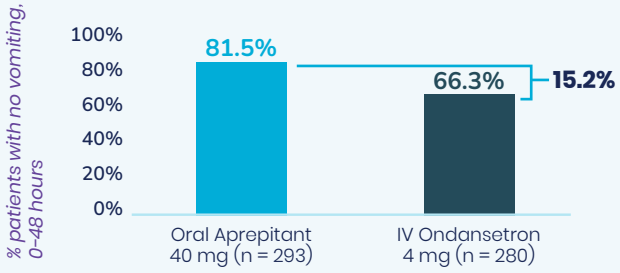
Study 2 Secondary Endpoint[1,3]



Aprepitant demonstrated superiority to IV ondansetron ($P < .001$[c]).

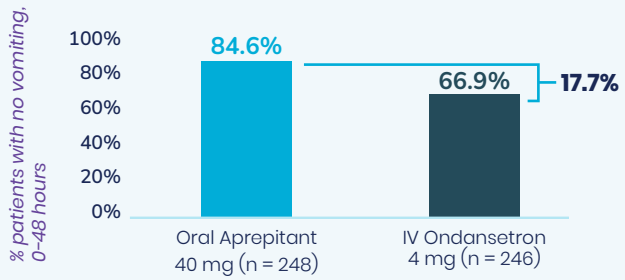
Superior Vomiting Prevention Through 48 Hours

Study 1 Secondary Endpoint[1,2]



- Aprepitant demonstrated superiority to IV ondansetron ($P < .001$[b])
- **Half as many patients vomited when treated with oral aprepitant** compared to IV ondansetron

Study 2 Secondary Endpoint[1,3]



- Aprepitant demonstrated superiority to IV ondansetron ($P < .001$[c])
- 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

Use in Specific Populations

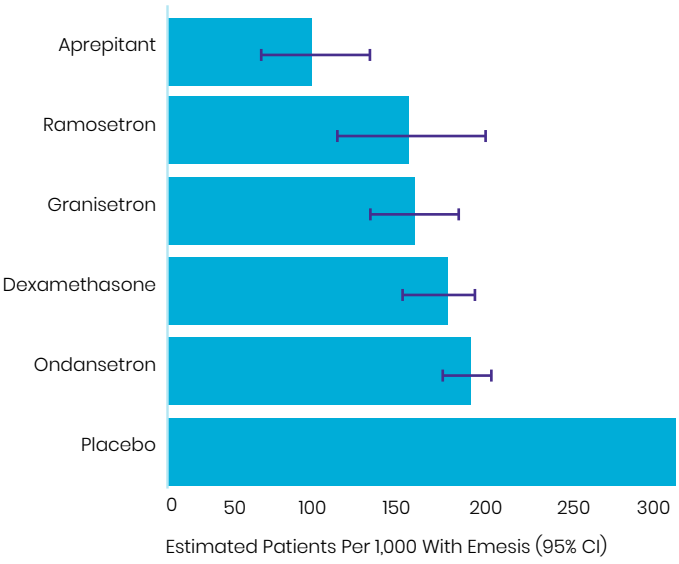
Avoid use of APONVIE in pregnant women as alcohol is an inactive ingredient in APONVIE. There is no safe level of alcohol exposure in pregnancy.

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

COCHRANE META-ANALYSIS: APREPITANT IS THE MOST EFFICACIOUS COMPOUND FOR THE PREVENTION OF VOMITING AFTER SURGERY WITH HIGH-CONFIDENCE EVIDENCE[6]

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.

Ranking of Most Effective Single-Agent Prophylactic With High-Confidence Evidence Through 24 Hours



Aprepitant-containing multimodal regimens were the most effective combinations

- The **most effective** combination contained aprepitant
- Aprepitant was included in **2 of the 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

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.

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APONVIE OFFERS A SAFETY PROFILE SIMILAR TO THAT OF IV ONDANSETRON

The active ingredient in APONVIE has been used for PONV since 2006.[21] 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]

Pooled Analysis: Adverse Reactions[1]

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

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

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.[22]

APONVIE IS PRICED TO SUPPORT BROAD ACCESS, WITH REIMBURSEMENT AND CONVENIENT PACKAGING AND DISTRIBUTION

- **WAC: $58.00 per vial**
- **Vial contains a single 32-mg dose**
- **340B: ≥23.1% discount**
- **Packaged in cartons of 10 vials**

Separate reimbursement from Medicare is expected in HOPDs and ASCs pending approval of 3-year transitional pass-through status (expected April 1, 2023).

- Discounts available under contracts with leading GPOs
- 340B and sub-WAC pricing available
- Refrigerated storage (2°C to 8°C [36°F to 46°F])[1]
  - Can remain at room temperature (20°C to 25°C [68°F to 77°F]) for up to 60 days[1]
- Distribution through authorized wholesalers and specialty distributors; prime vendor discounts apply

Note: Pricing as of November 8, 2022. 340B prices update quarterly. Confirm current pricing with your Heron representative.
WAC: wholesale acquisition cost.
GPO: group purchasing organization.

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PUSH PONV OUT OF YOUR PATIENTS' RECOVERY

APONVIE is a proven, effective antiemetic for the prevention of postoperative nausea and vomiting (PONV) that is delivered via a single IV push and offers a 48-hour effective duration. APONVIE was created to help patients experience a smooth recovery with less risk of PONV-related symptoms and may help hospital staff with patient throughput by reducing PONV-related interruptions.[1-3]

First and only IV NK_1 antagonist for prevention of PONV[1]

Superior vomiting prevention versus ondansetron through 48 hours[1-3,a]

Single IV push[1]

Comparable safety profile to IV ondansetron without QT prolongation[1]

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