Current Landscape on the Use of Antiemetics in Pharmacokinetic Bioequivalence Studies for Generic Drug Development

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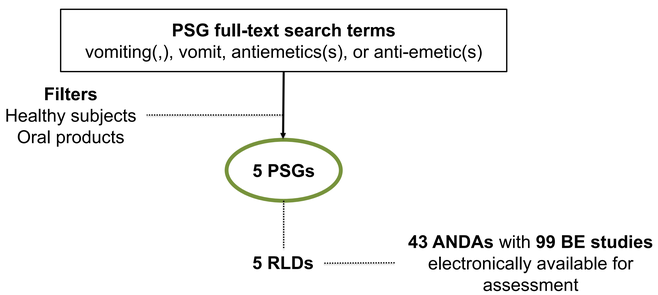
Introduction

- Gastrointestinal (GI) events such as nausea and vomiting are among the most commonly reported adverse reactions in bioequivalence (BE) studies conducted in healthy subjects and significantly affect their tolerability and compliance. Vomiting within a specific timeframe can impact absorption of oral drug products and increase the variability in pharmacokinetics (PK), potentially requiring removal of subjects from PK analysis to avoid confounding the BE conclusions. As such, mitigation strategies for vomiting in BE studies for high-emetogenic drugs may be crucial to subject retention and sample size estimation.
- This study evaluated the current landscape of mitigation strategies for vomiting in BE studies to inform standardized internal decision-making procedures on recommending the use of antiemetics in product-specific guidances (PSGs) for generic drug development.

Materials and Methods

A full-text search was performed to identify PSGs of oral drug products recommending healthy subject-based BE studies that contain wordings associated with antiemetics or vomiting, indicative of high emetogenicity. For the PSGs qualified for evaluation, available BE studies submitted in approved abbreviated new drug applications (ANDAs) for the corresponding reference listed drugs (RLDs) were reviewed to collect the following data: vomiting mitigation strategy, vomiting incidence, withdrawal rate due to vomiting, and alignment to the mitigation strategy recommended in the corresponding PSGs.



Results

- All five RLDs were approved with a titration scheme per labeling. The vomiting incidence was lower or comparable in healthy subjects in BE studies implementing PSG-recommended mitigation strategy(ies) for four out of five RLDs compared to the vomiting incidence in patients reported in the RLD labeling [Table 1].
- Most (95 out of 99) BE studies incorporated at minimum the mitigation strategy(ies) recommended in the respective PSGs [Figure 1].
- The antiemetics most commonly pre-specified on the protocol were ondansetron and promethazine [Figure 1]. Non-oral routes of administration (intramuscular, intravenous, or transdermal) were used for the majority of studies implementing antiemetics. The selection appeared to be based on the low risk of drug-drug interaction with study drugs and mechanism of drug-induced vomiting.

Results (cont.)

Table 1. Summary of Outcome from BE Studies that Implemented PSG-Recommended Vomiting Mitigation Strategy(ies)

		RLD Labeling			PSG Recommendations		Outcome from BE Studies Implementing Mitigation Strategy(ies) (n=95)	
Active Ingredient	**Dosage Form**	**Titration Scheme**	**Starting Dose**	**Vomiting (%)#**	**Vomiting Mitigation Strategy(ies)**	**BE Dose**	**Vomiting Rate (Mean ± SD %)**	**Withdrawal Rate Due to Vomiting (Mean ± SD %)**
Aripiprazole	Tablet	Yes	10 or 15 mg/day	11.0	Non-highest strength	10 mg x1	4.8 ± 4.2	4.0 ± 4.0
Aripiprazole	ODT	Yes	10 or 15 mg/day	11.0	Non-highest strength	10 mg x1	5.3 ± 5.6	5.3 ± 5.3
Donepezil HCl	Tablet	Yes	5 mg/day	9.2	Antiemetics	23 mg x1	21.8 ± 17.0	14.9 ± 11.5
Donepezil HCl; Memantine HCl	Capsule, ER	Yes	NA*	8.0; 2.0**	Antiemetics	10 mg; 28 mg x1	6.4 ± 3.0	6.4 ± 3.0
Selexipag	Tablet	Yes	0.2 mg BID	18.0	Antiemetics & Non-highest strength	0.4 mg x1	1.9 ± 2.5	1.9 ± 2.5

Abbreviations: SD, standard deviation; BID, twice daily; ER, extended-release; HCl, hydrochloride; NA, not applicable; ODT, oral disintegrating tablet.
#Antiemetic use unknown or as needed treatment only; pooled vomiting incidence at doses ≥ 2mg/day for RLDs of aripiprazole tablet and ODT; vomiting incidence at the highest studied dose for RLD of donepezil HCl tablet, donepezil HCl; memantine HCl tablet, and selexipag tablet.
*The combination is recommended for patients who were already stable on a titrated dose of donepezil HCl and memantine HCl.
**The vomiting incidence was 8% for donepezil HCl and 2% for memantine HCl.

Figure 1. Recommended vs. Implemented Vomiting Mitigation Strategy(ies) in Reviewed BE Studies (n=99 Studies)

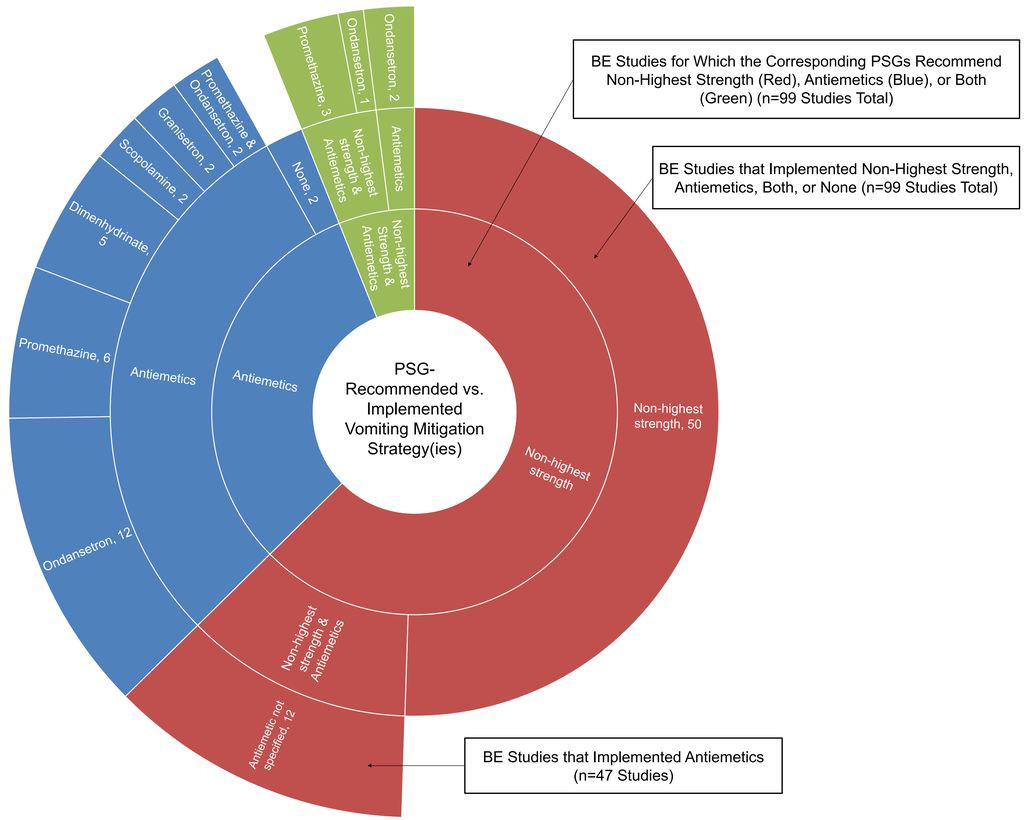


Table 2. Withdrawal Rate (Mean ± SD) due to Vomiting in BE Studies in Relation to Use of Antiemetics

	Donepezil HCl; Memantine HCl ER Capsule (n) *Highest strength*	Selexipag Tablet (n) *Non-highest strength*
With antiemetics	6.4% ± 3.0% (2)	1.9% ± 2.5% (2)
Without antiemetics	12.1% ± 6.4% (6)	45.1% ± 1.8% (4)

- Qualitative comparisons for selected RLDs showed significantly lower withdrawal rates due to vomiting reported in BE studies with implemented mitigation strategy(ies) vs. without [Table 2].

Interpretation and Conclusion

- Mitigation strategy(ies) for high-emetogenic drugs can be crucial in ensuring subject safety and preserving study power in BE studies.
- Drugs requiring titration for patient safety and tolerability may be associated with higher vomiting risk in BE studies compared to the RLDs' efficacy studies in patients. This may be attributed to the administration of the highest strength to treatment-naïve healthy subjects as generally recommended to maximize the detection of PK differences between test product and the RLD .
- Concomitant antiemetics could be a viable option to manage the risk of vomiting in BE studies at the highest strength, provided that they do not interact with the study drugs or interfere with bioanalytical methods.
- These findings will support the development of an optimal framework for recommending concomitant use of antiemetics in PSGs for generic drug development.

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