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APPLICATION NUMBER:

209589Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	209589
Link to EDR	Application 209589 - Sequence 0000 - 0000 (1) 01/31/2017 ORIG-1 /Multiple Categories/Subcategories
Submission Date	01/31/2017
Submission Type	Standard
Brand Name	Clenpiq™
Generic Name	Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid
Dosage Form and Strength	Solution/10 mg of sodium picosulfate, 3.5 g of magnesium oxide, and 12 g of anhydrous citric acid in 160 mL of solution
Route of Administration	Oral
Proposed Indication	Bowel preparation prior to colonoscopy
Applicant	Ferring Pharmaceuticals, Inc.
Associated IND(s)/NDA(s)	IND 101738, NDA 202535
OCP Reviewer	Xinyuan Zhang, Ph.D.
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1. EXECUTIVE SUMMARY

Ferring Pharmaceuticals Inc. (the applicant) is seeking approval of Clenpiq™ oral solution (160 mL) for cleansing of the colon as a preparation for colonoscopy in adults. The applicant is relying on the safety and efficacy of Prepopik, powder for oral solution (sodium picosulfate 10 mg, magnesium oxide 3.5 g, and anhydrous citric acid 12g, NDA 202535). The proposed product (Clenpiq) contains the same active ingredients and the same amount of each active ingredient as the reference product (Prepopik). Compared to the reference product, Clenpiq contains different excipients. The proposed dosage regimen is two doses for a complete preparation for colonoscopy using either the preferred method ('split-dose' method) or the alternative method ('day-before' method), and the same as the approved dosage regimen for the reference product.

The applicant submitted a biowaiver request for in vivo comparison of bioavailability based on the final presentation of each product being oral solution prior to administration. No clinical studies were conducted with Clenpiq.

In support of the biowaiver request, the applicant conducted three in vitro Caco-2 permeability studies to evaluate the potential effects of excipients on enterocyte integrity, and the oral absorption of the active ingredients. In in vitro permeability studies using Caco-2 cells, the permeability of active ingredients (Mg^{2+}, citric acid, and sodium picosulfate) and the active metabolite of picosulfate was not significantly different between Clenpiq and Prepopik when both products were applied as 20% solution. Although the study at 20% solution was considered reasonable based on the total amount of water to be taken with Clenpiq, it should be noted that the proposed label recommends drinking five 8 ounce cups of clear liquids (40 ounces total) within 5 hours and before bed after the 1st dose. Based on in vitro permeability studies using diluted solution, the difference in excipients between Clenpiq and Prepopik is not expected to result in significantly different oral absorption of active ingredients from Clenpiq compared to Prepopik.

Of note, according to the biopharmaceutics review, the initial difference in osmolality between Clenpiq and Prepopik is > 3-fold, and the osmolality becomes similar after dilution with three cups of clear liquid. Potentially higher osmolality could lead to better efficacy. Nevertheless, no clinical trial was conducted to evaluate the efficacy of Clenpiq. Refer to the biopharmaceutics review for details and the decision on the biowaiver.

1.1 Recommendations

The Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint. The sponsor proposed the consistent labeling for the clinical pharmacology related information and no differences were found between the proposed labeling and the labeling for the reference product (Prepopik).

1.2 Post-Marketing Requirements and Commitments

There is no post-marketing requirement (PMR) or post-marketing requirement commitment (PMC) from a clinical pharmacology perspective.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Clenpiq™ oral solution (160 mL) contains citric acid 12 g, magnesium oxide 3.5 g, and sodium picosulfate 10 mg. Magnesium oxide and citric acid react to create magnesium citrate in solution, which is an osmotic agent that causes water to be retained within the gastrointestinal tract. Sodium picosulfate is hydrolyzed by colonic bacteria to form an active metabolite: bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM, which acts directly on the colonic mucosa to stimulate colonic peristalsis. The stimulant laxative activity of sodium picosulfate together with the osmotic laxative activity of magnesium citrate produces a purgative effect which, when ingested with additional fluids, produces watery diarrhea[1].

There is no clinical pharmacokinetic (PK) study conducted for the proposed formulation. The sponsor relies on the previously approved Prepopik findings to inform the Clenpiq labeling concerning clinical pharmacology related sections. The PK properties are summarized in Table 1 based on Prepopik label[1] and clinical pharmacology review[2]. Although the dosage form is different between Prepopik and Clenpiq, because both products will be administered as oral solution, the dosage form difference is not expected to significantly affect the bioavailability of the active pharmaceutical ingredients (APIs) between the test and reference products. The clinical pharmacokinetics property of active ingredients of Clenpiq is expected to be similar to those of Prepopik.

Table 1: Summary of PK properties after oral administration of 2 doses (2 pouches separated by 6 hours) of Prepopik (sodium picosulfate 10 mg, magnesium oxide 3.5g, and anhydrous citric acid 12g) in 16 healthy subjects

PK parameters	Picosulfate (mean ± SD)	Mg^{2+}	BHPM*
Cmax	2.3 ± 1.4 ng/mL after the 1st dose 3.2 ± 2.6 ng/mL after the 2nd dose	1.9 mEq/L**	not detectable in majority of subjects
Tmax (hr)	1.9 ± 1.0 hours after the 1st dose 7.1 ± 2.1 hours after the 1st dose	10	NA
T1/2 (hr)	7.4		NA
Urine recovery	0.19%		0.01%

[1] Prepopik label (2012): https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202535lbl.pdf
[2] Jappar D. (2012): Prepopik clinical pharmacology review: http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8027c7ea

AUC_t (ng*h/mL)	37.81 ± 32.65 after both doses		NA
AUC_{inf} (ng*h/mL)	40.04 ± 32.54 after both doses		NA
DDIs	Sodium picosulfate did not inhibit the major CYP enzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5) evaluated. Based on an in vitro study using freshly isolated hepatocyte culture, sodium picosulfate is not an inducer of CYP1A2, CYP2B6, or CYP3A4/5.		

* Picosulfate is metabolized by bacteria in the colon to its active metabolite BHPM.
* * All magnesium levels were within the normal range (1.5-2.5mEq/L) throughout the study period.

There is no clinical pharmacology study submitted in this NDA. Three in vitro Caco-2 permeability studies were conducted to (1) investigate the impact of the test (Clenpiq) and reference (Prepopik) formulations on the Caco-2 cell monolayer integrity, and (2) compare the permeability of active ingredients and the active metabolite of picosulfate of the test and reference formulations. The applicant intended to use results from these studies together with additional evidence from other in vitro studies (reviewed by the Division of Biopharmaceutics) to support the biowaiver request. Refer to the biopharmaceutics review for the review of other in vitro study results.

Major findings from the in vitro Caco-2 permeability studies are the following.

- In general, solubility and permeability are two important factors affecting bioavailability besides first-pass metabolism. In this application, the apical-to-basolateral apparent permeability (Papp) of API components (Mg^{2+}, citric acid, and sodium picosulfate), and the active metabolite (BHPM) was similar across treatments (without excipients, in test formulation, and reference formulation). For these in vitro studies (17FERRNJP1, and 15FERRNJP1R8), Clenpiq 160 ml oral solution was diluted to a 20% test formulation and Prepopik was reconstituted as directed and diluted to a 20% reference formulation. The permeability of citric acid and picosulfate remained low and comparable to the permeability of atenolol, a low permeability probe drug, and the permeability of BHPM remained high. Apparent permeability of API components (Mg2+, citric acid, and sodium picosulfate) and BHPM was similar and the difference was generally within 2-fold between the test formulation and the reference formulation. As active ingredients of Clenpiq present as solution while the difference in excipients did not significantly affect the cell permeability after dilution, the difference in formulation is not expected to affect the oral absorption of active ingredients for Clenpiq compared to the reference product.

- In one in vitro study (15FERRNJP1R11) the cell membrane integrity was tested by the permeability of probe substrates (atenolol and minoxidol). When Clenpiq was applied as 30%, 50%, or 100 % solution, the permeability of atenolol increased as the incubation time

prolonged (beyond 40 minutes). This effect on the cell integrity was not observed with Prepopik and is attributable to the excipients in Clenpiq. The clinical relevance of this observation is unclear while the potential for clinically significant effects of Clenpiq on the GI tract appears to be low given the contact time between formulation and a specific area of the GI tract under clinical use should be brief compared to the in vitro experimental condition with a long incubation time with the Caco-2 cells. Nevertheless, according to the nonclinical review, there is no safety concern regarding the types and amounts of excipients used in the test formulation. Refer to the nonclinical review for details.

- Using the 20% diluent[3] for the subsequent permeability study for active ingredients seems reasonable because this product is recommended to be taken with a large amount of fluid (5 cups/40 ounces/1136 mL/12.3% solution within 5 hours for the 1st dose, and 3 cups/24 ounces/ 681.6 mL/19.0% solution for the 2nd dose) and the oral solution will be further diluted with fluid in the GI tract. It is noted that patients may not drink the recommended amount of liquid immediately.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Dosing regimen is the same as the approved reference product (Prepopik). (Source: draft labeling)

Split –dose dosage regimen (preferred method)	**Day-Before Dosage Regimen (alternative method)**
Dose 1 – On the day before colonoscopy: • Instruct patients to consume only clear liquids (no solid food or dairy) on the day before the colonoscopy up until 2 hours before the time of the colonoscopy. • Take the first dose (1 bottle) of CLENPIQ during the evening before the colonoscopy (e.g., 5:00 to 9:00 PM). • Follow CLENPIQ by drinking five 8 ounce cups (cup provided) of clear liquids (40 ounces total) within 5 hours and before bed. • If severe bloating, distention, or abdominal pain occurs, following the first dose, delay the second dose until the symptoms resolve.	Dose 1 – On the day before colonoscopy: • Instruct patients to consume only clear liquids (no solid food or dairy) on the day before the colonoscopy up until 2 hours before the time of the colonoscopy. • Take the first dose (1 bottle) of CLENPIQ in the afternoon or early evening before the colonoscopy (e.g., 4:00 to 6:00 PM). • Following the CLENPIQ dose, drink five 8 ounce cups (cup provided) of clear liquids (40 ounces total) within 5 hours and before the next dose. • If severe bloating, distention, or abdominal pain occurs, following the first dose, delay the second dose until the symptoms resolve.

[3] Samples were diluted with Hanks' balanced salt solution with the addition of D-glucose (HBSSg).

Dose 2 – Next morning on the day of colonoscopy (start approximately 5 hours prior to colonoscopy): • Continue to consume only clear liquids (no solid food or dairy). • Take the second dose (the second bottle) of CLENPIQ. • Following the CLENPIQ dose, drink at least three 8 ounce cups (cup provided) of clear liquids (24 ounces) at least 2 hours before the colonoscopy.	Dose 2 – Approximately 6 hours later in the evening the night before the colonoscopy (e.g., 10:00 PM to 12:00 AM): • Take the second dose (the second bottle) of CLENPIQ. • Following the CLENPIQ dose, drink three 8 ounce cups (cup provided) (24 ounces) of clear liquids within 5 hours and before bed.

2.2.2 Therapeutic individualization

Not applicable

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

In Section 7.1 ‘Drugs That May Increase Risks of Fluid and Electrolyte Abnormalities’, the following paragraph was removed as those were covered in the ‘Warnings and Precautions’ section (5.1, 5.2, 5.3, and 5.4).

(b) (4)

Section 12 ‘Clinical Pharmacology’ is the same as the reference product. Refer to the final approved labeling.

3. APPENDICES

3.1 Formulation Comparison (not to be disclosed under FOI)

Source: Pharmaceutical Development Report

Table 1 Comparative Composition of PREPOPIK and Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid Oral Solution

PREPOPIK® Powder for Oral Solution (approved under NDA 202535)		Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid Oral Solution	
Component	**Amount per Unit Dose**	**Component**	**Amount per Unit Dose**
Active Ingredients			
Sodium picosulfate	10 mg	Sodium picosulfate	10 mg
Magnesium oxide	3.5 mg	Magnesium oxide	3.5 mg
Anhydrous citric acid	12 g	Anhydrous citric acid	12 g
Inactive Ingredients			
Saccharin sodium	(b) (4)	Sodium benzoate	(b) (4)
Potassium hydrogen carbonate		Acesulfame potassium	
		Sucralose	
		Edetate disodium	
		Sodium metabisulfite	
		Sodium hydroxide	
		Malic acid	
		(b) (4) water	
Flavoring Agent			
(b) (4)		Cranberry flavor	

3.2 Review of Individual Studies

3.2.1 Study Number: 15FERRNJP1R8: Tolerability and Permeability in Caco-2 Cell Monolayer System of Sponsor's Test Articles, Formulated and Unformulated

Objective:

- To assess the impact of the test and reference formulations on the tolerability or Caco-2 cell monolayer integrity,
- To measure the permeability the API components (sodium picosulfate, citric acid, and magnesium) in the test and reference formulations, and unformulated API.

Study Design:

1. Treatments for tolerability or Caco-2 cell monolayer integrity study (source: Table 1 in study report 15FERRNJP1R8)

Table 1. Tolerability Treatments

Treatment	Apical	Basolateral
1	Formulation #2 (25%) with atenolol (100 µM) and minoxidil (10 µM) in HBSSg, pH 6.5	HBSSg, pH 7.4
2	Formulation #3 (25%) with atenolol (100 µM) and minoxidil (10 µM) in HBSSg, pH 6.5	HBSSg, pH 7.4
3	Atenolol (100 µM) and minoxidil (10 µM) in HBSSg, pH 6.5	HBSSg, pH 7.4
4	HBSSg, pH 6.5 (buffer control)	HBSSg, pH 7.4
(b) (4)		

2. The tolerability was assessed by measuring the permeability of atenolol (a moderate permeability probe), and minoxidil (a high permeability probe) in the absence and presence of the test and reference formulations.
3. Permeability study of the API components (sodium picosulfate, citric acid, and magnesium) in formulation #2, formulation #3, and unformulated API

Results:

1. Effect of 25% formulations #2 (Clenpiq, test) and 25% formulation #3 (Prepopik, reference) on Caco-2 permeability of atenolol and minoxidil (summary of Tables 2-8 in the study report), 'ref' in the table is the average atenolol or minoxidil permeability without formulations #2 or #3.

Interval	Formulation	Average Papp (10^6 cm/sec)		Ratios of Average Papp (N=4)		
		Atenolol	Minoxidil		Atenolol	Minoxidil
0-20 min	#2, 25%	0.767	3.665	#2, 25%/ref	7.5	3.9
	#3, 25%	0.116	1.075	#3, 25%/ref	1.1	1.2
	Atenolol (100 μM) or minoxidil (10 μM)	0.102	0.934	#2, 25%/#3, 25%	6.6	3.4
0-40 min	#2, 25%	0.675	4.040	#2, 25%/ref	3.2	1.3
	#3, 25%	0.194	2.715	#3, 25%/ref	0.9	0.9
	Atenolol (100 μM) or minoxidil (10 μM)	0.213	3.130	#2, 25%/#3, 25%	3.5	1.5
0-60 min	#2, 25%	0.667	3.863	#2, 25%/ref	3.4	1.1
	#3, 25%	0.121	2.140	#3, 25%/ref	0.6	0.6
	Atenolol (100 μM) or minoxidil (10 μM)	0.199	3.560	#2, 25%/#3, 25%	5.5	1.8
0-80 min	#2, 25%	0.765	4.248	#2, 25%/ref	3.9	1.1
	#3, 25%	0.150	2.775	#3, 25%/ref	0.8	0.7
	Atenolol (100 μM) or minoxidil (10 μM)	0.198	3.850	#2, 25%/#3, 25%	5.1	1.5
0-100 min	#2, 25%	0.837	4.315	#2, 25%/ref	4.2	1.0
	#3, 25%	0.176	3.185	#3, 25%/ref	0.9	0.8
	Atenolol (100 μM) or minoxidil (10 μM)	0.200	4.153	#2, 25%/#3, 25%	4.8	1.4
0-120 min	#2, 25%	0.964	4.455	#2, 25%/ref	4.5	1.0
	#3, 25%	0.179	3.153	#3, 25%/ref	0.8	0.7
	Atenolol (100 μM) or minoxidil (10 μM)	0.214	4.450	#2, 25%/#3, 25%	5.4	1.4

2. Summary of average Caco-2 permeability (10^{-6} cm/s, N=6) of sodium picosulfate, magnesium, and citric acid in 20% formulation #2 (Clenpiq, test), 20% formulation #3 (Prepopik, reference), and unformulated API; and Caco-2 permeability of atenolol and minoxidil co-administered with 20% formulation #2 (Clenpiq, test), 20% formulation #3 (Prepopik, reference), and unformulated API (summary of Tables 11-13 in the study report)

		Treatment*		
Analyte	**Conc. (µM)**	**2**	**3**	**4**
Sodium Picosulfate	26	0.459 ± 0.0547[a]	0.304 ± 0.101[a]	0.230 ± 0.0303
Citric Acid	78.1 mM	0.307 ± 0.0544	0.124 ± 0.0433 [a,b]	0.206 ± 0.0626
Citric Acid	78.1 mM		0.273 ± 0.0912[d]	0.360 ± 0.121[d]
Magnesium	108 mM	1.63 ± 0.371[c]	3.79 ± 0.629[a]	1.68 ± 0.231[c]
Magnesium	108 mM		2.65 ± 0.258	2.51 ± 0.339[a]
Minoxidil	10	5.01 ± 0.204	4.59 ± 0.286	4.85 ± 0.378
Minoxidil	10	4.59 ± 0.369	4.94 ± 1.10	4.21 ± 0.433
Minoxidil	10		5.09 ± 0.225	4.95 ± 0.171
Atenolol	100	0.307 ± 0.0546	0.171 ± 0.0309[a]	0.197 ± 0.0277
Atenolol	100	0.313 ± 0.0528	0.157 ± 0.0536	0.237 ± 0.0685
Atenolol	100		0.345 ± 0.0812	0.567 ± 0.191

*Treatment 2: 20% Formulation #2 (Clenpiq, test) in HBSSg, pH 6.5; Treatment 3: 20% Formulation #3 (Prepopik, reference) in HBSSg, pH 6.5; Treatment 4: unformulated API in HBSSg, pH 6.5

[a] One monolayer was excluded from calculations of mean and SD (n=5) for failed linearity (r^2 < 0.9 for cumulative concentration vs. time) or as a statistical outlier (failed the Q-test at the 90% confidence level).

[b] The measured dosing concentration of citric acid in Treatment 3 was only 35.5% of nominal, which resulted in very low calculated Papp, recovery, and % permeated values using the default method of normalizing to the nominal conc. Therefore, for citrate in Treatment 3, Papp, recovery, and % permeated were normalized to measured initial conc.

[c] Two or three monolayers were excluded from calculations of mean and SD for failed linearity (r^2 <0.9 for cumulative concentration vs. time); n=3 (Treatment 2) or n=4 (Treatment 4).

[d] Three monolayers failed linearity (r^2 < 0.9 for cumulative concentration vs. time) and were excluded from calculations of mean and SD; n=3.

Applicant's Conclusions

- For sodium picosulfate and citric acid, Papp and percent permeated were low, similar to the corresponding values for the co-dosed low-permeability reference compound atenolol. They were also similar across treatments, within a factor of 2 for sodium picosulfate and differing by slightly more than a factor of 2 for citric acid.
- For magnesium, Papp and percent permeated were similar across treatments and intermediate between those of atenolol and the co-dosed high permeability reference compound minoxidil.
- 20% dilution was selected because results indicated that integrity was maintained in the presence of the test formulations at ≤ 20% dilutions.

Reviewer's comments:

- It was noted that atenolol permeability was increased by more than 3-fold when it was co-incubated with formulation #2, 25% (Clenpiq, test) for all the time-intervals, while the change was less than 1.5-fold when it was co-incubated with formulation #3, 25%

(Prepopik, reference). Nevertheless, the increased permeability of atenolol is still less than 1×10^{-6} cm/sec.

- Basolateral pH was decreased from pH 7.4 to about 6.7 after incubation but the change was consistent among all the treatments.
- Multiple failures were excluded due to supralinear concentrations of citrate and atenolol measured at later time points, which may indicate compromised monolayer integrity at the later time points (experiments ran through 80 min).
- Permeability of sodium picosulfate, citric acid, and magnesium seemed similar across different preparations (formulation #2, formulation #3, and unformulated APIs) and the difference was generally within 2-fold.

3.2.2 Study Number: 15FERRNJP1R11: Tolerability of Caco-2 Cell Monolayers to Sponsor's Test Formulations

Objective: This is a non-GLP study to assess the Caco-2 cell monolayer tolerability of three dilutions of the test and reference formulations.

Study Design

1. Treatments: 30%, 50%, and 100% of formulation ELN000704 (Clenpiq, test), and 30%, 50%, and 100% of formulation ELN001946 (Prepopik, reference)
2. Similar study design as 15FERRNJP1R8 using different concentrations of the test and reference products.

Results (Source: Study report for 15FERRNJP1R11)

1. The tolerability study was conducted at higher product concentrations (30%, 50%, and 100% of each formulation) compared to formulations used in the tolerability study 15FERRNJP1R8. Similar trend was observed, i.e. atenolol permeability was increased when it was co-incubated with formulation ELN000704 (Clenpiq, test). The effect appeared to be dose-dependent.
2. At 100%, 50%, and 30% Formulation ELN000704 (Clenpiq, test), the integrity of all cell monolayers was acceptable after 20 minutes; monolayer integrity was acceptable at 100% and 30% after 40 minutes; and at least three of four monolayers failed at all dilutions at longer time points.
3. For 100%, 50%, and 30% formulation ELN001946 (Prepopik, reference), the integrity of all cell monolayers was acceptable at all the time points up to and including 120 minutes.
4. For all strengths of Formulation ELN000704 (Clenpiq, test), the measured apical pH was slightly (on average, up to approximately 0.3 units) higher than that of the buffer control, and the effect appeared to be dose-dependent.

5. For undiluted Formulation ELN001946 (Prepopik, reference), the measured apical pH was slightly (on average, approximately 0.2 units) higher than that of the buffer control; 50% and 30% Formulation ELN001946 had no impact on the pH.
6. Basolateral pH was decreased to about 6.8-6.9 from 7.4 for all treatments.

Reviewer's comments:

- It seems that the test formulation (solution) affects Caco-2 cell monolayer integrity at 100%, 50%, and 30% of unit strength. This is probably due to the excipients used in the test formulation. It is not clear how this effect will be translated into in vivo effect. Nevertheless, this product is recommended to be taken with a large amount of fluid (40 ounces/1136 mL/12.3% dilution within 5 hours for the 1st dose, and 24 ounces/ 681.6 mL/19.0% dilution for the 2nd dose). Therefore, using the data measured 20% dilution seems reasonable.

3.3.3 Study Number: 17FERRNJP1: In vitro Permeability Study of Mg^{2+}, Citrate, Sodium Picosulfate, and Bisacodyl Related Compound A in the Presence and Absence of Excipients, According to the biopharmaceutics Classification System (BCS) Guidances Issued by the United States Food and Drug Administration

Objective: To assess the in vitro permeability of API components (Mg^{2+}, citric acid, and sodium picosulfate), and BHPM (picosulfate's active metabolite: bis(p-hydroxyphenyl)-2-pyridylmethane) in the test and reference formulations, and APIs without excipients.

Study Design:[4]

Permeability (10^{-6} cm/sec) in Caco-2 system was measured for Mg^{2+}, citric acid, sodium picosulfate, and BHPM in different concentrations of formulation 1 (Clenpiq, test), and formulation 2 (Prepopik, reference).

Results:[5]

Summary of A-to-B Permeability of Mg^{2+}, citric acid, sodium picosulfate, BHPM, and atenolol and minoxidil co-dosed with testing formulations (source: Tables 4-7 in study 17FERRNJP1 report)

[4] Module 4.2.2.2 Study report for 17FERRNJP1: \\cdsesub1\evsprod\nda209589\0000\m4\42-stud-rep\422-pk\4222-absorp\17ferrnjp1\17ferrnjp1-pre-clinical-study-report.pdf
[5] Module 4.2.2.2 Study report for 17FERRNJP1: \\cdsesub1\evsprod\nda209589\0000\m4\42-stud-rep\422-pk\4222-absorp\17ferrnjp1\17ferrnjp1-pre-clinical-study-report.pdf

Table 4. A-to-B Permeability of Mg^{++} and Co-dosed Reference Compounds

Nominal MgO Dosing Conc. (mM)			54.3	81.4	108
Strength			10%	15%	20%
Formulation	**Analyte**	**Parameter**			
Unformulated	**Mg^{++}**	P_{app} (10^{-6} cm/s)	2.75 ± 0.146	1.74 ± 0.106	1.82 ± 0.134
		Recovery (%)	149 ± 13.6	117 ± 3.06	130 ± 11.7
		% Permeated	9.26 ± 0.210	6.66 ± 0.833	5.11 ± 0.112
	Minoxidil	P_{app} (10^{-6} cm/s)	5.19 ± 0.243	5.10 ± 0.196	4.82 ± 0.133
		Recovery (%)	94.3 ± 1.93	92.5 ± 2.51	91.6 ± 1.56
	Atenolol	P_{app} (10^{-6} cm/s)	0.207 ± 0.0300	0.318 ± 0.0941	1.52 ± 0.0651*
		Recovery (%)	98.5 ± 2.81	97.5 ± 3.60	98.1 ± 6.29
Formulation 1	**Mg^{++}**	P_{app} (10^{-6} cm/s)	1.76 ± 0.658	2.37 ± 0.155	2.33 ± 0.166
		Recovery (%)	115 ± 6.11	132 ± 20.5	104 ± 8.27
		% Permeated	5.11 ± 0.783	6.79 ± 0.179	7.56 ± 0.716
	Minoxidil	P_{app} (10^{-6} cm/s)	4.74 ± 0.290	5.00 ± 0.314	5.13 ± 0.141
		Recovery (%)	78.5 ± 1.75	89.5 ± 2.38	88.1 ± 1.19
	Atenolol	P_{app} (10^{-6} cm/s)	1.46 ± 0.0621*	0.519 ± 0.0542	0.381 ± 0.0295
		Recovery (%)	79.5 ± 2.28	89.2 ± 3.60	83.8 ± 3.29
Formulation 2	**Mg^{++}**	P_{app} (10^{-6} cm/s)	2.42 ± 0.113	1.74 ± 0.0771	1.11 ± 0.0683
		Recovery (%)	119 ± 5.04	99.9 ± 15.8	88.6 ± 3.04
		% Permeated	8.16 ± 0.131	5.38 ± 0.0435	3.30 ± 0.0425
	Minoxidil	P_{app} (10^{-6} cm/s)	4.85 ± 0.191	4.68 ± 0.186	3.50 ± 0.160
		Recovery (%)	92.2 ± 3.05	92.4 ± 2.80	91.6 ± 1.63
	Atenolol	P_{app} (10^{-6} cm/s)	0.126 ± 0.0179	0.156 ± 0.0261	0.266 ± 0.0174
		Recovery (%)	88.7 ± 3.94	93.2 ± 3.20	93.4 ± 3.29

All results are from the initial permeability experiment (18-Nov-2016; see Table 3), in which atenolol and minoxidil were co-dosed with the test articles to monitor cell monolayer integrity.

* All six replicates failed the monolayer integrity test based on the P_{app} of co-dosed atenolol, but the results are reported to enable comparison with other treatments.

Table 5. A-to-B Permeability of Citric Acid

Nominal Citric Acid Dosing Conc. (mM)			39.0	58.6	78.1
Strength			10%	15%	20%
Unformulated	Citric Acid	P_{app} (10^{-6} cm/s)	0.183 ± 0.00859[a]	0.177 ± 0.0548	0.159 ± 0.0299
		Recovery (%)	92.8 ± 3.45[a]	96.9 ± 7.70	90.6 ± 8.74
		% Permeated	0.281 ± 0.0518[a]	0.303 ± 0.0.0990	0.231 ± 0.0445
	Minoxidil*	P_{app} (10^{-6} cm/s)	2.99 ± 0.339	2.54 ± 0.278	4.30 ± 0.277
	Atenolol*	P_{app} (10^{-6} cm/s)	0.540 ± 0.0920	0.451 ± 0.103	0.400 ± 0.0396
Formulation 1	Citric Acid	P_{app} (10^{-6} cm/s)	0.238 ± 0.0238[a]	0.260 ± 0.0119	0.285 ± 0.0479[a]
		Recovery (%)	100 ± 7.72[a]	89.7 ± 4.48	71.2 ± 8.37[a]
		% Permeated	0.332 ± 0.0262[a]	0.383 ± 0.0304	0.391 ± 0.0619[a]
	Minoxidil*	P_{app} (10^{-6} cm/s)	4.05 ± 0.414	2.80 ± 0.153	3.14 ± 0.179
	Atenolol*	P_{app} (10^{-6} cm/s)	0.770 ± 0.113	0.902 ± 0.0474	1.28 ± 0.0237
Formulation 2	Citric Acid	P_{app} (10^{-6} cm/s)	0.124 ± 0.0155	0.148 ± 0.0174	0.184 ± 0.0383
		Recovery (%)	86.0 ± 5.76	93.0 ± 10.8	82.4 ± 11.5
		% Permeated	0.190 ± 0.0178	0.224 ± 0.0256	0.296 ± 0.0447
	Minoxidil*	P_{app} (10^{-6} cm/s)	2.28 ± 0.0491	2.30 ± 0.465	4.48 ± 0.293
	Atenolol*	P_{app} (10^{-6} cm/s)	0.263 ± 0.0298	0.328 ± 0.0495	0.523 ± 0.0280

* All results are from the repeat permeability experiment (5-Dec-2016; see Table 3), in which atenolol and minoxidil were not co-dosed and cell monolayer integrity was monitored by a PE test.

[a] One replicate was excluded from calculation of mean and SD; n=5. See Table A25 (Treatment 1, 10% unformulated), Table A28 (Treatment 4, 10% Formulation 1), and Table A30 (Treatment 6, 20% Formulation 2).

Table 6. A-to-B Permeability of Sodium Picosulfate

Nominal Sodium Picosulfate Dosing Conc. (μM)			13.0*	19.5#	26.0*
Strength			10%	15%	20%
Unformulated	Picosulfate	P_{app} (10^{-6} cm/s)	0.242 ± 0.0586[a,b]	0.196 ± 0.0215[b]	0.177 ± 0.0398[b]
		Recovery (%)	99.0 ± 9.91[b]	84.7 ± 10.4[b]	104 ± 6.49[b]
		% Permeated	0.328 ± 0.0795[b]	0.188 ± 0.0157[b]	0.281 ± 0.0694
	Minoxidil	P_{app} (10^{-6} cm/s)	2.99 ± 0.339	5.10 ± 0.196	4.30 ± 0.277
	Atenolol	P_{app} (10^{-6} cm/s)	0.540 ± 0.0920	0.318 ± 0.0941	0.400 ± 0.0396
Formulation 1	Picosulfate	P_{app} (10^{-6} cm/s)	0.254 ± 0.0671[b]	0.506 ± 0.0359[b]	0.329 ± 0.0610
		Recovery (%)	81.2 ± 6.37[b]	79.9 ± 7.70[b]	73.3 ± 5.20
		% Permeated	0.387 ± 0.0617[b]	0.435 ± 0.0802	0.454 ± 0.0967[b]
	Minoxidil	P_{app} (10^{-6} cm/s)	4.05 ± 0.414	5.00 ± 0.314	3.14 ± 0.179
	Atenolol	P_{app} (10^{-6} cm/s)	0.770 ± 0.113	0.519 ± 0.0542	1.28 ± 0.0237
Formulation 2	Picosulfate	P_{app} (10^{-6} cm/s)	0.189 ± 0.0198	0.149 ± 0.0392	0.173 ± 0.0209
		Recovery (%)	92.5 ± 4.17	99.9 ± 10.1	85.5 ± 1.97
		% Permeated	0.256 ± 0.0268	0.156 ± 0.0452	0.279 ± 0.0168
	Minoxidil	P_{app} (10^{-6} cm/s)	2.28 ± 0.0491	4.68 ± 0.186	4.48 ± 0.293
	Atenolol	P_{app} (10^{-6} cm/s)	0.263 ± 0.0298	0.156 ± 0.0261	0.523 ± 0.0280

* The reported results are from the repeat permeability experiment (5-Dec-2016; see Table 3), in which atenolol and minoxidil were not co-dosed and cell monolayer integrity was monitored by a PE test.

The reported results are from the initial permeability experiment (18-Nov-2016; see Table 3), in which atenolol and minoxidil were co-dosed with the test articles to monitor cell monolayer integrity.

[a] Calculated using only the final (100 min) receiver concentration.

[b] One or two replicates were excluded from calculation of mean and SD; n=4 or 5. See Table A43 (Treatment 1, 10% unformulated), Table A44 (Treatment 2, 15% unformulated), Table A45 (Treatment 3, 20% unformulated), Table A46 (Treatment 4, 10% Formulation 1), Table A47 (Treatment 5, 15% Formulation 1), and Table A48 (Treatment 6, 20% Formulation 1).

Table 7. A-to-B Permeability of BHPM

Nominal BHPM Dosing Conc. (µM)			1.30	2.60	13.0
Strength			1%	2%	10%
Unformulated	BHPM	P_{app} (10^{-6} cm/s)	27.7 ± 3.75	29.0 ± 1.93	31.0 ± 2.22
		Recovery (%)	108 ± 7.59	83.3 ± 4.23	101 ± 5.14
		% Permeated	39.8 ± 4.57	41.5 ± 3.57	46.7 ± 3.69
	Minoxidil*	P_{app} (10^{-6} cm/s)	3.06 ± 0.396	2.52 ± 0.211	2.42 ± 0.195
	Atenolol*	P_{app} (10^{-6} cm/s)	0.379 ± 0.0918	0.374 ± 0.0476	0.193 ± 0.0347
Formulation 1	BHPM	P_{app} (10^{-6} cm/s)	54.8 ± 2.96	38.6 ± 3.70	29.5 ± 1.67
		Recovery (%)	144 ± 10.2	84.7 ± 7.10	104 ± 5.81
		% Permeated	87.1 ± 3.64	54.9 ± 5.41	48.5 ± 2.36
	Minoxidil*	P_{app} (10^{-6} cm/s)	3.92 ± 0.593	5.44 ± 0.325	4.74 ± 1.28
	Atenolol*	P_{app} (10^{-6} cm/s)	0.832 ± 0.175	2.11 ± 0.213	1.96 ± 1.18
Formulation 2	BHPM	P_{app} (10^{-6} cm/s)	48.9 ± 6.21	33.6 ± 2.44	28.8 ± 1.52
		Recovery (%)	131 ± 13.6	112 ± 8.78	103 ± 3.45
		% Permeated	77.2 ± 11.2	52.2 ± 3.99	46.1 ± 1.93
	Minoxidil*	P_{app} (10^{-6} cm/s)	1.53 ± 0.182	1.54 ± 0.158	2.71 ± 0.0614
	Atenolol*	P_{app} (10^{-6} cm/s)	0.162 ± 0.0251	0.265 ± 0.0231	0.385 ± 0.00701

* All results are from the repeat permeability experiment (13-Dec-2016; see Table 3), in which atenolol and minoxidil were not co-dosed and cell monolayer integrity was monitored by a PE test.

Applicant's Conclusions

1. In general, the A-to-B Papp of four analytes (Mg^{2+}, citric acid, sodium picosulfate, and BHPM) was similar across treatments (without excipients and in both test and reference formulations) and across dosing concentrations up to 20% dilution.
2. The Papp of BHPM was high, the Papp of citric acid and sodium picosulfate was low (similar to that of atenolol), and the Papp of Mg^{2+} was intermediate.

Reviewer's comments:

- As observed in studies15FERRNJP1R11 and 15FERRNJP1R8, the test formulation (Clenpiq) may decrease the Caco-2 cell monolayer integrity in a dose dependent manner. Therefore, the A-to-B Papp and % permeated of four analytes (Mg^{2+}, citric acid, sodium picosulfate, and BHPM) was slightly higher in formulation 1 than in unformulated and formulation 2 but generally within 2-fold.

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/s/

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11/02/2017

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