CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210166Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210166
PDUFA Goal Date	December 21, 2018
OSE RCM #	2018-192
Reviewer Name(s)	Charlotte Jones, MD, PhD, MSPH
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	December 13, 2018
Subject	Evaluation of Need for a REMS
Established Name	Prucalopride
Trade Name	Motegrity
Name of Applicant	Shire Development LLC
Therapeutic Class	Serotonin 4 (5-HT4) receptor agonist with prokinetic activity
Formulation(s)	Oral immediate release tablets 1mg and 2mg
Dosing Regimen	Adults: 2 mg orally daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Motegrity (prucalopride) is necessary to ensure the benefits outweigh its risks. Shire Development LLC (Shire) submitted a New Drug Application (NDA) for Prucalopride with the proposed indication for the treatment of chronic idiopathic constipation in adults. The risks associated with prucalopride include the potential for major adverse cardiac events and suicide. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Gastrointestinal and Inborn Error Products (DGIEP) agree that a REMS is not needed to ensure the benefits of prucalopride outweigh its risks. The risk for major adverse cardiac events and suicide were not found to be a significant risk for prucalopride, however both risks will be addressed in labeling. The benefit profile for a large population of patients and rarity of serious risks support the conclusion that a REMS is not necessary to ensure that benefits outweigh risks for prucalopride.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Motegrity (prucalopride) is necessary to ensure the benefits outweigh its risks.[a] Shire Development LLC (Shire) submitted a New Drug Application (NDA) 210166 for prucalopride with the proposed indication for the treatment of chronic idiopathic constipation in adults. This application is under review in the Division of Gastrointestinal and Inborn Error Products. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Motegrity (prucalopride), a new molecular entity, is a high affinity serotonin (5HT4) receptor agonist proposed for the treatment of chronic idiopathic constipation. It is a prokinetic agent that stimulates peristalsis, increasing bowel motility.[1] Prucalopride is proposed as 1 and 2 mg oral tablets. Adults are to take 2 mg orally once daily; patients with severe renal impairment are to take 1 mg orally daily. Prucalopride was approved in the European Union in 2009 under the name Resolor with no additional risk minimization activities in place and is currently approved in 60 countries including, Switzerland, Canada, China and Japan.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210166 relevant to this review:

- 12/21/2017: NDA 210166submission for treatment of chronic constipation received.
- 05/29/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Prucalopride
- 10/18/2018: Gastrointestinal Advisory Committee (AC) Meeting convened to discuss Prucalopride. The AC voted 10/0 in favor of approval.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Chronic idiopathic constipation (CIC) is a functional constipation associated with symptoms of straining, lumpy/hard stools, incomplete evacuation, sensation of anorectal obstruction, <= 3 defecations/week, and requiring manual maneuvers for defecation in greater than 25% of bowel movements. Chronic idiopathic constipation has a prevalence of 14- 20% in the United States and 45% of sufferers report having the condition for 5 years or more.[2-4b,c] Chronic idiopathic constipation has a significant impact on patients. CIC can lead to social isolation since symptoms are associated with eating. Additionally, there may be fear that symptoms will recur, and patients experience frustration due to the lack of effective therapies and lack of empathy of family and friends for this distressing condition.[2d] The agency recognizes a need for additional treatment options for patients with CIC.[5]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are FDA approved products for the treatment of CIC. Additionally, there are products endorsed by the American College of Gastroenterology for the management of chronic constipation (Table 1). The use of polyethylene glycol (PEG) is one of the mainstays of treatment. However, the label for PEG recommends use be limited to 7 days, a significant limitation due to the chronic nature of CIC where years of treatment may prove necessary. Biofeedback is effective for patients with pelvic floor

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

dyssynergia. Non-FDA approved treatments of uncertain benefit include fiber supplementation and hydration.[6]

Table 1 Summary of therapies for chronic idiopathic constipation

Product Trade Name (Generic) **Year of Approval**	**Indication**	**Dosing/Administration**	**Important Safety and Tolerability Issues**	**Risk Management Approaches/** **Boxed Warning, Medication Guide**	
FDA Approved Treatments					
Polyethylene Glycol OTC 2008	Occasional constipation	17 g dissolved in 4-8 ounces of water. Use once a day, no more than 7 days	May cause loose, watery stools.		
Linaclotide 2012	Chronic idiopathic constipation in adults	145 mcg capsules once daily orally	Diarrhea	Boxed warning for severe diarrhea in children	
Lubiprostone 2006	Chronic idiopathic constipation in adults	24 mcg capsules twice daily orally	Nausea Diarrhea Syncope Dyspnea Not to be used in setting of bowel obstruction		
Plecanatide 2017	Chronic idiopathic constipation in adults	3 mg capsule oral once daily	Diarrhea	Boxed warning for risk of serious dehydration in children. Contraindicated in children < 6	

				years of age.	
Other Treatments Biofeedback may be effective in patients with pelvic floor dyssynergia. Fiber supplements and hydration are widely recommended but of uncertain benefit.					

4 Benefit Assessment

The efficacy of prucalopride for the adjunctive treatment of CIC in adults was demonstrated in two pivotal phase 3 studies, supported in 3 additional studies and a 4th that failed to show efficacy but contributed safety data (see Appended Table 1 for additional details and NCT numbers).[e] The studies were similar in design: randomized, double-blind, and placebo-controlled. Each of these studies had the same primary efficacy endpoint: the number of patients with ≥ 3 spontaneous complete bowel movements (SCBM) per week based on patient diary. The studies beyond the primary studies were required to show the generalizability to the US population as the primary studies skewed Asian and male m respectively. The clinical reviewer concluded all of the trials achieved statistical significance, except for SPD-555-401, which did not achieve statistical significance at week 12 or 24 (Table 2).[6] Additionally, the efficacy for prucalopride was also shown with the FDA's currently recommended efficacy endpoint; the trials demonstrated a treatment benefit of prucalopride over placebo with 6-16% of patients being a responder for ≥ 9 out of 12 weeks. A SCBM weekly responder is a patient who has a SCBM weekly frequency ≥3 and increased by ≥1 weekly from baseline.[5]

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

Table 2 Primary Efficacy Analysis Results for Phase ¾ Studies (ITT/mITT Population)

	PLA		PRU ≤2 mg		Percent Difference PRU–PLA	
Study	**N**	**n (%)**	**N**	**n (%)**	**(95% CI)**	**P-value[1]**
PRU-CRC-3001*	252	26 (10.3)	249	83 (33.3)	23 (16.1, 30)	<0.0001
SPD555-302*	181	32 (17.7)	177	67 (37.9)	20.2 (11, 29.2)	<0.0001
PRU-INT-6	240	23 (9.6)	236	46 (19.5)	9.9 (4, 16)	0.002
PRU-USA-11	193	25 (13.0)	190	55 (28.9)	16 (8, 24)	<0.001
PRU-USA-13	212	25 (11.8)	214	50 (23.4)	11.6 (4, 19)	0.0015
SPD-555-401	169	34 (20.1)	171	43 (25.1)	5 (-3.9, 13.9)	0.341

Source: Table 2 on Page 13 of the draft-labeling-text.pdf and Applicant's IR response on March 30, 2018, verified by the reviewer.
Abbreviations: CI, confidence interval; PLA, placebo; PRU, prucalopride
[1] P-value based on primary analyses method for each study. Note that the proportions of subjects on PRU <2 mg were 46% (79 of 177) for Study 302 and 15% (30 of 171) for Study 401.

*primary trials

5 Risk Assessment & Safe-Use Conditions

Although the integrated safety database included 86 trials that have been completed in the drug's development program worldwide, for the purposes of this review the Agency focused on 16 completed double-blind, placebo-controlled, phase 2-through 4 trials of at least 4 weeks duration in adult patients with CIC (Pool D in the sponsors safety base (Appended Table 2)).[5] The most common treatment emergent adverse events were headaches, abdominal pain, nausea, and diarrhea.[6] Patients continued on treatment for up to 18 months in open label studies, with headache and GI difficulties leading to discontinuation in 5%.[7]

5.1 DEATHS

Seven deaths occurred in prucalopride treated patients based on analysis of the integrated safety database. The causes of death included lobar pneumonia, respiratory failure, bronchitis, myocardial infarction (2) events), and suicide (2). None of the deaths were attributed to the study drug by the investigator and the clinical reviewer agrees with this assessment. There were no deaths in the 6 combined pivotal and supplemental trials.[1]

5.2 MAJOR ADVERSE CARDIOVASCULAR EVENTS

Prucalopride is in the same class of serotonin 5HT4 agonists as tegaserod, which was removed from the market because a 2007 safety analysis found an increased risk of heart attack, stroke, and unstable angina (heart/chest pain) in patients treated with tegaserod compared with treatment with an inactive substance (placebo).[8] Prucalopride data shows that it is a more selective agonist for 5HT4 receptors than tegaserod, without the 5HT1 activity that tegaserod has.[5,9]

In lieu of a pre-market CV safety trial, the Agency agreed that the Applicant could conduct a long-term, observational, pharmacoepidemiology study (SPD555-802) because prucalopride has been approved by EMA since 2009. SPD555-802 followed a protocol for a post-marketing retrospective cohort (observational) study to measure the incidence of Major Adverse Cardiovascular Events (MACE) in European patients with exposure to prucalopride (PRU) or polyethylene glycol 3350 (PEG).
Designed to exclude a three-fold risk from prucalopride, the primary analysis pooled results from studies separately conducted in four European data sources. This primary analysis estimated MACE incidence in PRU versus PEG with a standardized incidence rate ratio (SIRR) of 0.64, 95% confidence interval (CI) 0.36 to 1.13. Subgroup analysis in ≥55-year-old men estimated risk from prucalopride at a SIRR 2.57, 95% CI 0.71 to 9.29. Declaring results otherwise consistent across pre-specified primary, secondary, subgroup, and sensitivity analyses, the investigators for SPD555-802 concluded by finding "no evidence of an increased risk of MACE in patients with chronic constipation using prucalopride as compared with PEG."

Study SPD555-802 is considered as supportive in the context of the totality of the safety data from controlled trials. The division of epidemiology (DEPI) reviewer concluded that there was no signal for MACE in SPD55-802, the observational study showed a standardized incidence risk ratio for MACE in Prucalopride treated patients vs. PEG treated patients of 0.64, 95% CI 0.36-1.13. However, thet Agency determined that "because of a concern about serious risk of bias due to confounding, FDA placed low confidence in the quantitative result, i.e., SIRR 0.64, from the SPD555-802 primary analysis. Interpreting this quantitative result as causally valid, a patient starting treatment might expect to suffer a 36% lower incidence of a subsequent major cardiovascular event, if started on prucalopride instead of PEG. However, the serious risk of bias due to confounding demanded more cautious interpretation."

The DEPI reviewer concludes "In summary, FDA accepted the findings from SPD555-802 as evidence that reasonably excludes a greater than three-fold MACE risk for prucalopride use compared to PEG. Because of the serious potential for bias due to confounding, FDA could not use SPD555-802 to reliably bound MACE risk at levels lower than three-fold." [5 page 60, f]

5.3 SUICIDE

There was 1 attempted suicide in the placebo-controlled trials in the prucalopride arm and none in the placebo arm. There were 2 completed suicides and 4 attempted suicides in the 4476 subjects in the entire safety database.[1 g]

There is a single report of hallucinations and suicidality temporally associated with suicide in the literature however the patient was also on medication that can cause serotonin syndrome. However,

[f] The Advisory Committee voted 10 to 0 that the Applicant had adequately address the potential cardiovascular risks of Prucalopride on October 18, 2018. The cardiac safety analysis will be included in the clinical trial experience in the labeling.

[g] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

according to the clinical reviewer, an overall increased risk of depression and psychiatric adverse events was not seen in the safety data.[6]

As prucalopride has been approved for multiple years outside of the US, three reports of post-marketing psychiatric events, a Medicines and Healthcare products Regulatory Agency (MHRA) post marketing safety update report as well as a draft publication from the Uppsala (safety) Monitoring Centre triggered inquiries into psychiatric symptoms/suicides.[10] These inquiries concluded that no changes to the reference safety information were recommended. However, even as the MHRA inquiry did not conclude there were required changes to information as well as no overall increased risk, as there were cases seen in the trials for prucalopride, the Agency has determined that Prucalopride will include a Warning/Precaution for Suicidal Ideation/Behavior.

6 Expected Postmarket Use

Chronic idiopathic constipation is a common disorder affecting the adult population. Patients are likely to be treated by multiple prescriber types including generalists and mid-level providers in inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond routine pharmacovigilance and labeling. The Applicant is proposing a medication guide.[11]

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Prucalopride on the basis of the efficacy and safety information currently available.

Chronic idiopathic constipation is a common, long lasting and distressing condition for patients with significant impact on quality of life.

Prucalopride has been shown in multiple studies to have a positive clinical benefit. The theoretical risks of major cardiac events and suicide based on drug class were not evident in the clinical trials for Prucalopride. Additionally, Prucalopride is widely used outside the US with no safety restrictions and no significant safety signals identified.

Labeling will be used to inform prescribers and patients of the common risks of headache and gastrointestinal problems as well as the potential risks of suicide and MACE.

The overall limited and infrequent if present serious risks of prucalopride in the setting of a large population likely to benefit from treatment does not require a REMS to ensure that benefits outweigh risks.

9 Conclusion & Recommendations

Based on the current review and available data, the benefit-risk profile is favorable therefore, a REMS is not necessary for Prucalopride to ensure the benefits outweigh the risks. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

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6. Line C. DGIEP for NDA 210166 Mid Cycle Meeting Internal Team Meeting Presentation. (May 21, 2018).
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8. Zelnorm (tegaserod maleate) information. *Postmarket Drug Safety Information for Patients and Providers* https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm. Accessed September 21, 2018.
9. SHIRE. NDA 210166 Prucalopride NonClinical Overview (December 21, 2017).
10. Gasparotto A. Prucalopride and Suicidal Ideation. *WHO Pharmaceuticals Newsletter.* 2015;3:22-25.
11. SHIRE. NDA 210166 Risk Management Plan (Non-REMS). (December 21, 2017).

10.2 APPENDED TABLES

Appended Table 1 Key trials in Prucalopride Application

STUDY	Duration	Study Type	Dose	Study Size	Demographics	Primary Endpoint
PRU-CRD-3001* NCT 01116206	12wk	R, DB, PC E &S&QOL	Pru 2mg Placebo	N=501	Asian Adults 90% Female	% of subjects 3≥SCBM/week over entire study period
SPD555-302* NCT 01147926	12wk	R, DB, PC E&S&QOL	Pru 2mg** Placebo	N=374	European adult males 97% white	% of subjects ≥3SCBM/week over entire study period
PRU-INT-6 NCT 00488137	12wk	R, DB, PC E&S&QOL	Pru 2mg Pru 4mg Placebo	N=720	91% Female 93% White	Percentage of patients with an average of ≥ 3 SCBM/week.
PRU-USA-11 NCT 00483886	12wk	R, DB, PC E&S&QOL	Pru 2mg Pru 4mg Placebo	N=628	88% Female 90% White	Percentage of patients with an average of ≥ 3 SCBM/week
PRU-USA-13 NCT 00485940	12wk	R, DB, PC E&S&QOL	Pru 2mg Pru 4mg Placebo	N=651	87% Female 88% White	Percentage of patients with an average of ≥ 3 SCBM/week
SPD-555-401# NCT 01424228	24wk	R, DB, PC, E&S&QOL		N=360	85% Female 93% White	Percentage of subjects with an average weekly frequency of ≥ 3 SCBM per week

R=Randomized, DB=Double Blind, PC=Placebo controlled, E&S&QOL=Efficacy and Safety and Quality of Life Study

SCBM=Spontaneous Complete Bowel Movement

*Primary trials others are supportive

**Patients greater than 65 years of age started at 1mg with option to increase to 2mg

#This study failed to show clinical efficacy but was the long term (24 week) safety study conducted for the EU.

Appended Table 2 Trials in Pool D used in Safety Analysis

	PLA N = 1973	PRU 0.5 mg N = 110	PRU 1 mg N = 330	PRU 2 mg N = 1516	PRU 4 mg N = 1349	Total PRU N = 3305	Total N = 5278
				n (%)			
All studies	1973	110	330	1516	1349	3305	5278
PRU-INT-6	240 (12.2)	0	0	238 (15.7)	238 (17.6)	476 (14.4)	716 (13.6)
PRU-USA-13	212 (10.7)	0	0	214 (14.1)	215 (15.9)	429 (13.0)	641 (12.1)
PRU-USA-11	209 (10.6)	0	0	207 (13.7)	204 (15.1)	411 (12.4)	620 (11.7)
PRU-USA-28	257 (13.0)	0	0	0	253 (18.8)	253 (7.7)	510 (9.7)
PRU-CRC-3001	252 (12.8)	0	0	249 (16.4)	0	249 (7.5)	501 (9.5)
PRU-INT-12	72 (3.6)	0	76 (23.0)	75 (4.9)	80 (5.9)	231 (7.0)	303 (5.7)
PRU-USA-25	117 (5.9)	0	0	0	225 (16.7)	225 (6.8)	342 (6.5)
PRU-INT-2	63 (3.2)	0	67 (20.3)	62 (4.1)	61 (4.5)	190 (5.7)	253 (4.8)
PRU-USA-3	46 (2.3)	43 (39.1)	48 (14.5)	48 (3.2)	46 (3.4)	185 (5.6)	231 (4.4)
SPD555-302	186 (9.4)	0	15 (4.5)	169 (11.1)	0	184 (5.6)	370 (7.0)
SPD555-401	180 (9.1)	0	7 (2.1)	174 (11.5)	0	181 (5.5)	361 (6.8)
PRU-INT-1	45 (2.3)	46 (41.8)	43 (13.0)	40 (2.6)	0	129 (3.9)	174 (3.3)
PRU-USA-26	18 (<1)	21 (19.1)	24 (7.3)	26 (1.7)	0	71 (2.1)	89 (1.7)
PRU-GBR-4	38 (1.9)	0	39 (11.8)	0	0	39 (1.2)	77 (1.5)
PRU-BEL-6	26 (1.3)	0	0	0	27 (2.0)	27 (<1)	53 (1.0)
PRU-FRA-1	12 (<1)	0	11 (3.3)	14 (<1)	0	25 (<1)	37 (<1)

PLA = placebo; PRU = prucalopride

Note: Percentages were based on all subjects in the safety set for Phase 2-4 double-blind, placebo-controlled studies of ≥ 4 weeks duration

Source: Applicant table, Integrated Summary of Safety, Table 12, page 106/504[1]

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