CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
2Q17 April – May

BRAND NAME
Trulance™

GENERIC NAME
Plecanatide

MANUFACTURER
Synergy Pharmaceuticals, Inc.

DATE OF APPROVAL
January 19, 2017

PRODUCT LAUNCH DATE
Anticipated in 1Q2017

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastics, antipsychotics, antiretrovirals, and immunosuppressants)

FDA APPROVED INDICATION(S)[1]
The treatment of chronic idiopathic constipation (CIC) in adult patients.

OFF-LABEL USES
Irritable bowel syndrome characterized by constipation (IBS-C)

CLINICAL EFFICACY[2]
The safety and efficacy of Trulance in 1,397 patients with CIC was evaluated in a randomized phase III, multicenter, double-blind, placebo-controlled study. The primary efficacy endpoint was the percentage of patients who were durable overall complete spontaneous bowel movement (CSBM) responders over the 12-week treatment period. Secondary and additional endpoints reported from the bowel movement diary included frequency of CSBMs and spontaneous bowel

movements (SBMs) within 24 hours after the first dose of study medication and stool consistency from the Bristol Stool Form Scale (BSFS) score for each bowel movement.

Following the informed consent, patients entered a screening period. The last 2 weeks of the screening period consisted of a pre-treatment assessment period to confirm eligibility and establish each patient's baseline for efficacy outcome measurements. Patients were instructed to record their daily bowel movements, stool consistency scores, and abdominal symptoms in an electronic diary. Patients who maintained eligibility at the end of the 2-week pretreatment assessment were randomized on day 1 of the 12-week treatment period in a 1:1:1 ratio to receive either Trulance 3 mg or Trulance 6 mg or placebo orally once daily for 12 weeks. At weeks 4, 8, and 12 of the treatment period and 2 weeks following the last dose of medication (week 14), patients returned to the clinic to undergo efficacy and safety assessments.

Both doses of Trulance resulted in a significantly greater percentage of durable overall CSBM responders (21.0%, 3 mg; 19.5%, 6 mg) as compared with placebo (10.2%; P <0.001 for both). Both Trulance doses significantly improved all secondary and additional efficacy endpoints. Trulance 3 mg and 6 mg significantly increased mean weekly CSBM frequency from baseline (increase of 2.5 and 2.2/week, respectively) vs. placebo (1.2/week; P <0.001 for both) and mean weekly SBM frequency (increase of 3.2 and 3.1/week, respectively) vs. placebo (1.3/week; P <0.001, for both) over the 12-week treatment period.

Since Trulance 6 mg once daily did not demonstrate additional treatment benefit and had a greater incidence of adverse reactions, the Trulance 6 mg dose is not recommended for treatment of CIC.

CONTRAINDICATIONS
Trulance is contraindicated in:

- Patients younger than 6 years of age
- Known or suspected mechanical gastrointestinal obstruction

BLACK BOX WARNINGS
Risk of serious dehydration in pediatric patients: Avoid the use of Trulance in patients 6 years to less than 18 years of age.

DRUG INTERACTIONS
Not applicable

ADVERSE REACTIONS
The majority of adverse events observed in the published trial were mild to moderate in severity. A total of 15 patients experienced a serious adverse event across treatment groups: 6 with Trulance 3 mg, 5 with Trulance 6 mg, and 4 with placebo. Of the serious adverse events reported, diverticulitis (placebo group) was the only one considered to be possibly related to the

study drug. The rate of discontinuing study medication due to an adverse event was 5.1% with Trulance 3 mg, 5.3% with Trulance 6 mg, and 1.3% with placebo. The most common adverse event, diarrhea, occurred in 1.3% (placebo), 5.9% (3 mg) and 5.7% (6 mg) of patients.

Adverse reactions reported in less than 2% of Trulance treated patients and with an incidence greater than placebo were: sinusitis, upper respiratory tract infection, abdominal distension, flatulence, abdominal tenderness, and increased liver biochemical tests (2 patients with alanine aminotransferase (ALT) greater than 5 to 15 times the upper limit of normal and 3 patients with aspartate aminotransferase (AST) greater than 5 times the upper limit of normal).

DOSAGE AND ADMINISTRATION
The recommended dosage of Trulance is 3 mg orally once daily with or without food.

PRODUCT AVAILABILITY
Tablets: 3 mg

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
linaclotide (Linzess®)	72 mcg or 145 mcg PO QD	
lubiprostone (Amitiza)	24 mcg PO BID	
Lactulose	15-30 ml PO QD	
Senokot® (sennosides)	Two 8.6 mg tabs PO QD-BID	
Metamucil® (psyllium)	One rounded tsp in 8 oz liquid PO up to TID	
Dulcolax® (bisacodyl)	5 to 15 mg PO or 10 mg PR QD	
FiberCon® (Calcium polycarbophil)	Two 625 mg tabs PO QD-QID	5000 mg PO daily
Citrucel® (Methylcellulose)	Caplet: 2 caplets PO up to 6 times daily Powder: 2 grams in 8 oz of cold water PO up to 3 times daily	12 caplets PO daily 6 grams daily
MiraLax® (Polyethylene glycol 3350)	17 grams in 4-8 oz water PO once daily	17 grams per day Duration of treatment: 2 weeks
Colace® (Docusate sodium)	50-200 mg PO QD-QID	200 mg PO daily

Boldface indicates generic availability

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Utilization Management Recommendation
• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): i) To prevent inappropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes (1) Trulance is being evaluated in clinical trials for irritable bowel syndrome characterized by constipation (IBS-C) ii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison
• CPAC score: 53 vs. Linzess - Equal therapeutic outcomes anticipated • Equal therapeutic outcomes are anticipated for Trulance and Linzess; therefore, it would be appropriate to provide equal access to both or to require a trial of one before the other. • It would be clinically appropriate to require a trial of two laxative agents (bulk-forming, emollients, osmotic and/or stimulant) prior to the initiation of Trulance.

REFERENCES

[1] Trulance™ [package insert]. New York, NY: Synergy Pharmaceuticals Inc., January 2017.

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[2] Miner PB, Koltun WD, Wiener GJ, et al. A randomized Phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. The American Journal of Gastroenterology. February 2017. doi:10.1038/ajg.2016.611. Accessed February 7, 2017.