Prucalopride

The drug pipeline is flush with new drug options for chronic constipation

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(first) Seminar
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Functional Constipation

- Women > men
- Characterized by any of:
  - Persistent difficult
  - Seemingly incomplete defecation
  - Infrequent BM (once ≤ Q3-4d)

Rome II

- Modified Rome II criteria
  - ≤ 2 spontaneous bowel movements/week
  - hard stools,
  - sensation of incomplete evacuation, and
  - straining on at least 25% BM

Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut*. 2011;60:209-218.

Treatment options

- Lifestyle: increase
  - Dietary fiber
  - Fluid intake
  - Exercise
- Laxatives
  - Bulking agents:
    - Methylcellulose
    - Psyllium
  - Stool softeners:
    - Docusate
  - Osmotic:
    - Lactulose
    - PEG
    - MOM
  - Stimulant:
    - Senna
    - Bisacodyl

Dissatisfaction with Laxatives

- 44–50% lack of efficacy
- 50–67% inadequate symptom relief
- 44–68% not satisfied with QOL improvement

Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. Aliment Pharmacol Ther 2007;25:599–608

Pharmacologic Options

- Cisapride
- Tegaserod
- Prucalopride (RESOTRAN™)
- Lubiprostone
- Linaclotide

Pharmacologic Options

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Pharmacologic Options

- Cisapride
- Tegaserod
- **Prucalopride (RESOTRAN™)**
- Lubiprostone
- Linaclotide

MOA

- 5-HT_4 agonist
  - Enhances peristaltic reflex
  - Propulsive motor patterns
- Effects:
  - Increases motility
    - Proximal colonic & gastroduodenal
  - Improves gastric emptying
  - Induces giant migrating contractions

Delay to market

- MESH Term : 2000
- Toxicology Review 1999 – 2003
  - Cisapride
    - Human ether-a-go-go-related gene (hERG)
      - QT prolongation & ventricular arrhythmias
  - Tegaserod
    - 5-HT_1 = CV ischemic events
- Sale from J&J to Movetis 2003 – 2006
- Movetis bought by Shire 2010
- Drug licensed to Janssen for NA sales
- NOC : 2011 (Europe since 2009)

de Maeyer JH, Lefebvre RA, Schuurkes JAJ. 5-HT_4 receptor agonists: similar but not the same. *Neurogastroenterol Motil* (2008) 20, 99–112

Clinical Question

P	Adults with chronic constipation who have failed previous laxative therapy
I	Prucalopride
C	Placebo
O	Efficacy -# Spontaneous Complete Bowel Movements -Mean Change SCBM -Patient satisfaction Safety

Search Strategy

Databases	Pubmed, Google, Google Scholar, Embase, IPA, Cochrane
Search	Prucalopride AND chronic constipation
Limits	English, Human, Adult
Results	RCT 12 • Excluded 2 for opioid/CNS etiology • Remainder included in SR Systematic Review 5 • Include 1 Meta-analysis, 1 review • Excluded 2 expert opinion 1 CNS etiology

Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief

M Pennant,* R Orlando, P Barton, S Bayliss, K Routh and C Meads

Health Technology Assessment 2011; Vol. 15: Suppl. 1

Pennant M,. Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief. *Health Technol Assess*. 2011;15 Suppl 1:43-50

NHS Review

Design	License application (9 studies)
P	Adult women with laxative refractory constipation
I	Prucalopride
C	Placebo
O	Efficacy - Proportion ≥3 SCBM/week - Economic evaluation

Pennant M,. Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief. *Health Technol Assess*. 2011;15 Suppl 1:43-50

PAC-QOL

Table 1 | Patient Assessment of Constipation-Quality of Life satisfaction scale
Item
1) Fewer bowel movements than you would like
2) Satisfied with how often you have a bowel movement
3) Satisfied with the regularity of your bowel movements
4) Satisfied with the time it takes for food to pass through the intestines
5) Satisfied with your treatment
Likert Score (0–4)
Score 4 indicating not at all/none of the time satisfied
Score 3 indicating a little bit/a little bit of the time satisfied
Score 2 indicating moderately/some of the time satisfied
Score 1 indicating quite a bit/most of the time satisfied
Score 0 indicating extremely/all of the time satisfied

- Score Range 0-4
- MCSD = 0.5
  - Trials use 1
- Baseline
  - Overall
    - 2.1 – 2.3
  - Satisfaction
    - 3.1 – 3.4

Pennant M,. Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief. *Health Technol Assess*. 2011;15 Suppl 1:43-50

Results

	Prucalopride n (%)	Placebo n (%)	Abs Diff	NNT BL
Patients with ≥3 SCBM/week	181 (25.4)	87 (12.2)	13.2	8
Patients with increase ≥1 SCBM/week	308 (45)	177 (24.4)	19.5	5
Mean change SCBM / week	1.9	1.2	0.7	0-1 = 60% 1-3 = 30%
Overall mean PAC-QOL score	1.33	1.68	0.35	2.1 – 2.3

Pennant M,. Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief. *Health Technol Assess*. 2011;15 Suppl 1:43-50

Critique

- No evidence of efficacy in "target population"
  - 2 trials recruited refractory patients
  - 17% of patients in "pivotal trial"
- Included opioid induced constipation
- 2 trials report out to 18 months, "high attrition of >60%" so not included

Pennant M,. Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief. *Health Technol Assess*. 2011;15 Suppl 1:43-50

Summary

- 20% of patients had at least 1 more SCBM/week
- Drop in efficacy comparing

1-4 weeks (32%) vs 1-12 weeks (26%)

  - ?Clinically significant
  - PAC-QOL satisfaction score same ~2.44
    - -0.96 from baseline

- Did not address ADE

Pennant M,. Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief. *Health Technol Assess*. 2011;15 Suppl 1:43-50

Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis

Alexander C Ford,[1,2] Nicole C Suares[1]

Gut 2011;**60**:209–218.

Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut*. 2011;60:209-218.

Ford 2011

Design	SR & MA of RCT (7 trials for prucalopride)	
P	Chronic Idiopathic Constipation	
I	Prucalopride 0.5, 1, 2, 4mg	
C	Placebo	
O	Efficacy • P: Tx failure OR Mean stools per week • S: effects on individual CIC Sx	Toxicity • ADE due to therapy

Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut*. 2011;60:209-218.

Ford 2011

- Medline, Embase, Cochrane
- RCT, CIC, vs placebo
- Used ROME I, II, or III
- 7 trials total for prucalopride
- 6 trials allowed rescue laxatives
- 2 trials recruited patients resistant or dissatisfied with laxatives

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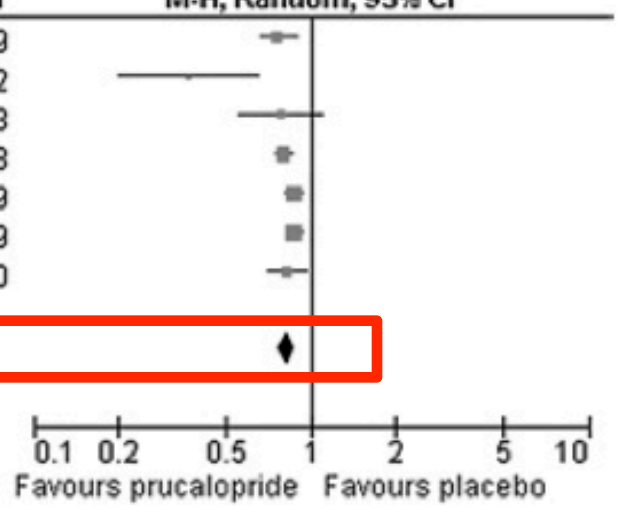
Primary Endpoint ≥3 SCBM

Study or Subgroup	Prucalopride Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Miner 1999	121	183	40	46	12.9%	0.76 [0.65, 0.89]	1999
Emmanuel 2002	10	39	27	38	1.5%	0.36 [0.20, 0.64]	2002
Coremans 2003	17	27	21	26	3.8%	0.78 [0.55, 1.10]	2003
Camilleri 2008	289	411	184	209	21.9%	0.80 [0.74, 0.87]	2008
Quigley 2009	331	429	187	212	23.3%	0.87 [0.81, 0.94]	2009
Tack 2009	374	476	217	240	24.5%	0.87 [0.82, 0.92]	2009
Muller-Lissner 2010	146	231	55	72	12.0%	0.83 [0.70, 0.97]	2010
Total (95% CI)		**1796**		**843**	**100.0%**	**0.82 [0.76, 0.88]**	
Total events	1288		731				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.98$, $df = 6$ ($P = 0.02$); $I^2 = 60\%$

Test for overall effect: $Z = 5.36$ ($P < 0.00001$)



- NNT 6

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Sensitivity Analysis

Table 4 Sensitivity analyses of efficacy of prucalopride in chronic idiopathic constipation.

	Number of studies	Number of subjects	RR of failure to respond to therapy	95% CI	I^2 value	Number needed to treat	95% CI
All studies	7	2639	0.82	0.76 to 0.88	60%	6	5 to 9
Risk of bias of trials							
Low	3	1564	0.84	0.79 to 0.89	29%	7	5 to 10
High	4	1075	0.75	0.61 to 0.92	77%	5	3 to 11
Definition of CIC							
Rome II criteria	6	2562	0.84	0.81 to 0.88	13%	7	6 to 9
Other criteria	1	77	0.36	0.20 to 0.64	N/A	2	1.5 to 4
Duration of therapy							
≤4 weeks	4	662	0.73	0.60 to 0.90	64%	4	3 to 10
>4 weeks	3	1977	0.85	0.81 to 0.90	42%	8	6 to 11
Definition of response to therapy							
≥3 CSBMs per week	5	2509	0.84	0.80 to 0.88	28%	7	6 to 9
Other definition	2	130	0.55	0.24 to 1.25	84%	N/A	N/A
Dose of prucalopride used							
1 mg od	3	319	0.68	0.46 to 1.00	82%	N/A	N/A
2 mg od	5	1560	0.85	0.80 to 0.90	18%	8	6 to 11
4 mg od	6	1615	0.83	0.77 to 0.90	52%	6	5 to 11

N/A, not applicable; CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; od, once daily.

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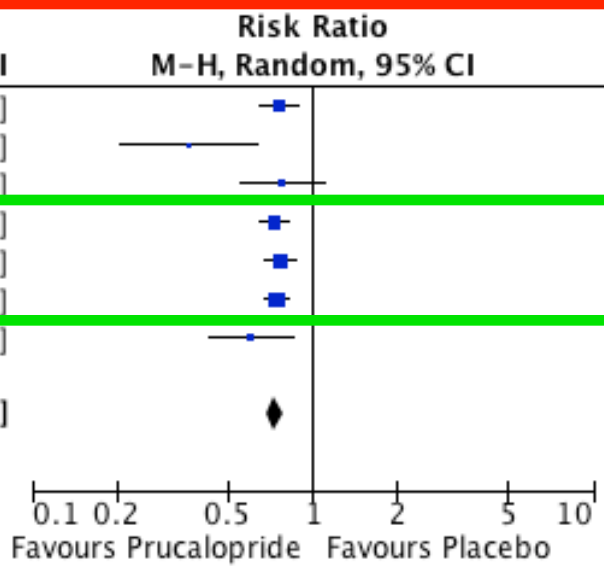
≥1 SCBM over baseline

Study or Subgroup	Prucalopride Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1999 Miner	121	183	40	46	16.9%	0.76 [0.65, 0.89]
2002 EMMANUEL	10	39	27	38	1.7%	0.36 [0.20, 0.64]
2003 Cormans	17	27	21	26	4.4%	0.78 [0.55, 1.10]
2008 Camilleri	220	411	153	209	22.5%	0.73 [0.65, 0.83]
2009 Quigley	229	413	150	207	22.8%	0.77 [0.68, 0.86]
2009 Tack	259	439	185	234	27.3%	0.75 [0.67, 0.83]
2010 MULLER-LISSNER	60	231	31	72	4.4%	0.60 [0.43, 0.85]
Total (95% CI)		**1743**		**832**	**100.0%**	**0.73 [0.68, 0.79]**
Total events	916		607			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.31$, df = 6 (P = 0.22); $I^2 = 28\%$

Test for overall effect: Z = 8.03 (P < 0.00001)



- NNT = 5

Mean Change from Baseline SCBM/week

- Prucalopride = 2.2
- Placebo = 1.1

Adverse Events

ADE	RR	CI (95%)	NNH	Baseline
Overall	1.14	1.05 – 1.24	10	
Headache	1.70	1.25 – 2.31	8	
Nausea	1.98	1.39 – 2.82	6	
Diarrhea	2.72	1.80 – 4.13	3	
Serious	0.88	0.58 – 1.34		2.7%

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Critique

- "2 or 4 mg is optimal dose"
  - Pool all doses together
- Only assessed primary outcome
  - ≥ 3 SCBM
  - ? ≥ 1 SCBM
  - ? Mean change SCBM

Summary

- 2 trials recruited patients previously failed conventional therapy
- NNT 5 : ≥1 SCBM/week
- NNH 10 : All Adverse effects

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Overall Summary

EFFICACY	
# SCBM	≥ 3 = NNT 6 ≥ 1 = NNT 5
Patient satisfaction	PAC-QOL score decreased from 3.25 to 2.55
Mean change SCBM/week	2 for prucalopride 1 for placebo
SAFETY (NNH)	
Overall	10
Headache	8
Nausea	6
Diarrhea	3

Overall Summary

- Tachyphylaxis not seen
- Re-treatment possible for responders
- Trials showed efficacy after 4 week
  - If not effective by then, stop

Overall Critique

- Trials industry funded
  - Funnel plot
- 2 trials recruited patients who failed conventional therapy
  - ?evidence to support

Health Canada Indication

- Chronic idiopathic constipation in
- Adult female patients
- In whom laxatives failed to provide adequate relief
  - "There were an insufficient number of male patients in the clinical trials to demonstrate efficacy"

Place in therapy

- Conventional therapy available
- Uncomfortable condition
- Expensive treatment
- Bottom line: Use in patients that have failed conventional therapy

Future Study and Other applications

- Efficacy in males
- Prucalopride for bowel prep
- Use in Palliative Care
- Non-cancer opioid induced constipation
- Spinal Cord Injury associated constipation
- Cochrane Review for Chronic Constipation
- Pediatrics