NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA211; Prucalopride for the treatment of chronic constipation in women

This guidance was issued in December 2010.

The review date for this guidance is October 2013.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit

"To appraise the clinical and cost effectiveness of prucalopride within its licensed indication for the treatment of chronic constipation in women in whom laxatives fail to provide adequate relief".

3. Current guidance

1.1. Prucalopride is recommended as an option for the treatment of chronic constipation only in women for whom treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered.

1.2. If treatment with prucalopride is not effective after 4 weeks, the woman should be re-examined and the benefit of continuing treatment reconsidered.

1.3. Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, who has carefully reviewed the woman's previous courses of laxative treatments specified in 1.1.

4. Rationale[1]

The few new studies available on the long-term safety and efficacy of prucalopride in women will not change the recommendations. The TA211 guidance should therefore be transferred to the static list. The remit of TA211 is for chronic constipation in women, and would need to be expanded to include the planned marketing authorisation extension for prucalopride [redacted]

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

[redacted] should be considered in topic selection for referral as an STA.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2010 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Prucalopride is currently licensed for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. The marketing authorisation for prucalopride has not changed since publication of TA211, however prucalopride is currently in phase III trials for the treatment of chronic constipation in men which were expected to have been completed in September 2013.

[redacted]. In addition, a phase III trial on use of prucalopride in people aged 6 to 17 was completed in March this year.

No new interventions or comparators have come to market since the original guidance was issued.

The manufacturer has highlighted several studies which have relevance to TA211. A pan Asia-Pacific double-blind placebo-controlled study (PRUCRC3001) evaluated 501 patients with chronic constipation and demonstrated that 2 mg prucalopride would improve normalisation of bowel movements over a 12-week period compared with placebo. The manufacturer suggests that these results confirm the safety and efficacy findings seen in the European registration studies (PRU-INT-6, PRU-USA-11 and PRU-USA-13) which were considered as part of TA211. The manufacturer has also highlighted the publication (Tack et al. 2013) of an integrated analysis of the three European registration studies to update the SPC with the population modelled in the original cost-effectiveness analysis.

In the literature searches, four systematic reviews were identified. Brenner et al. (2013) evaluated the efficacy of mu-opioid receptor antagonists , lubiprostone and prucalopride and concluded that mu-opioid receptor antagonists are safe and effective for opioid-induced constipation but that there was not enough evidence to allow further assessment of prucalopride. Other systematic reviews identified (Cheng

2012; Ford and Suares 2011; Gatta et al 2013) all concluded that prucalopride is effective compared with placebo.

A small randomised controlled study comparing macrogol/polyethylene glycol 3350 with prucalopride for treating chronic constipation was identified (Cinca et al 2013). The study contained 240 patients and concluded comparable efficacy between the two interventions, with better tolerability observed with macrogol/PEG3350.

Several studies evaluating long-term tolerability of prucalopride were identified and largely support the recommendations in TA211.

The currently published evidence is not likely to lead to a change in the recommendations of the original guidance

8. Implementation

A submission from Implementation is included in Appendix 3.

Based on the implementation advice, the data strongly suggests that the recommendations in TA211 are being adhered to given the steady increase in the prescribing prucalopride since publication of the appraisal guidance.

9. Equality issues

No equality issues were raised during the original appraisal.

GE paper sign off: Frances Sutcliffe, 14 October 2013

Contributors to this paper:

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care. Clinical Guideline CG61. Issued: February 2008. Sections of this guideline are currently being updated.

Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. Clinical Guideline CG140. Issued: May 2012. Review date: May 2015.

Irritable bowel syndrome with constipation in adults: linaclotide. Evidence Summary: New Medicine ENM16. Issued: April 2013.

Suspended/terminated

Methylnaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care. Technology Appraisal TA277. Terminated due to non-submission in March 2013.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.	No change. Prucalopride is currently in phase III trials for the treatment of chronic constipation in men. A phase III trial on use in people aged 6 to 17 was completed in March this year.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Bevenopran (Cubist)	Phase III for opioid induced constipation
Dexloxiglumide (Rottapharm)	Phase III for constipation associated with irritable bowel syndrome
Elobixbat (Ferring)	Phase III for chronic idiopathic constipation
Lubiprostone (Sucampo)	Licensed in the UK for chronic idiopathic constipation. An application for a further

Drug (manufacturer)	Details (phase of development, expected launch date,)
	indication (opioid- induced constipation) is anticipated around Q4, 2013.
Naloxegol (AstraZeneca)	Phase III for opioid-induced constipation. European regulatory filings anticipated Q3 2013.
Plecanatide (Synergy)	Phase III for chronic, idiopathic constipation.

Registered, unpublished and terminated trials

Trial name and registration number	Details
Prucalopride Effects on Subjects With Chronic Non-cancer Pain Suffering From Opioid Induced Constipation NCT01117051; M0001-C301; SPD555-301.	n=169 *"The study was stopped by the sponsor based on a non-safety related business priority decision"* Results at termination available at clinicaltrials.gov.
A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Prucalopride (Resolor) Tablets in Subjects With Chronic Constipation NCT01116206; CR017173.	n = 507 Completed ~March 2011.
Study to Investigate Prucalopride vs. Polyethylene Glycol 3350 on Colon Activity NCT01707667; SPD555-403.	n = 12 Estimated completion date: October 2013.
Evaluation of Long-term Prucalopride Treatment With Chronic Constipation in Subjects Aged ≥ 18 Years NCT01424228; M0001-C401.	n = 364 Completed ~ December 2012 Male and female participants included.

References

Brenner DM, Ford AC, Schoenfeld PS (2013) **Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: Systematic review and meta-analysis**. *Gastroenterology.Conference: Digestive Disease Week 2013, DDW 2013 Orlando, FL United States.Conference Start: 20130518 Conference End: 20130521.Conference Publication: (var.pagings).144 (5 SUPPL.1) (pp S215), 2013.Date of Publication: May 2013.*

Cheng E (2012) **Efficacy of prucalopride in the treatment of chronic constipation: A systematic review and meta-analysis of randomized controlled trials**. *Clinical Gastroenterology and Hepatology.Conference: AGA Clinical Congress: Practice, Evidence, and Quality in 2012 Miami Beach, FL United States.Conference Start: 20120120 Conference End: 20120121.Conference Publication: (var.pagings).10 (3) (pp 329*

Cinca R, Chera D, Gruss HJ et al. (May 2013) **Randomised clinical trial: macrogol/PEG 3350+electrolytes versus prucalopride in the treatment of chronic constipation -- a comparison in a controlled environment**. *Alimentary Pharmacology & Therapeutics* 37 (9): 876-886
Ford AC, Suares NC (2011) **Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: Systematic review and meta-analysis**. *Gut.60 (2) (pp 209-218), 2011.Date of Publication: February 2011.* (2): 209-218.

Gatta L, Kerstens R, Scarpignato C (2013) **How effective is prucalopride for the treatment of chronic constipation? A systematic review and meta-analysis**. *Gastroenterology.Conference: Digestive Disease Week 2013, DDW 2013 Orlando, FL United States.Conference Start: 20130518 Conference End: 20130521.Conference Publication: (var.pagings).144 (5 SUPPL.1) (pp S547-S548), 2013.Date of Publication: May 2013*

Tack J, Quigley E, Camilleri M et al. (2013) **Efficacy and safety of oral prucalopride in women with chronic constipation in whom laxatives have failed: an integrated analysis**. *United European Gastroenterology* 1 (1): 48-59-.

Appendix 3 – Implementation submission

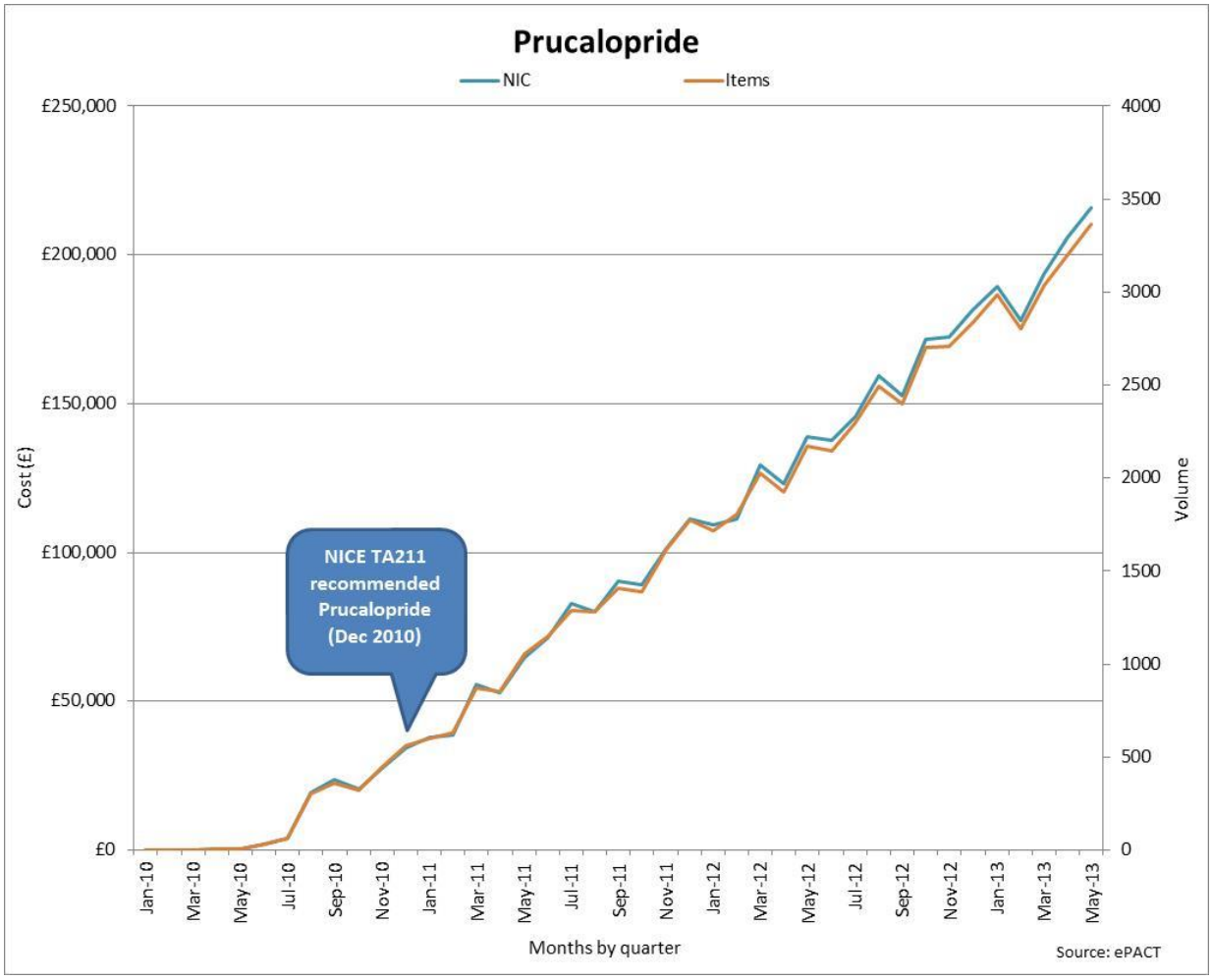
Contents

1. Routine healthcare activity data

1.1. ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost and volume of Prucalopride prescribed in primary care and in hospitals that has been dispensed in the community in England between January 2010 and May 2013.

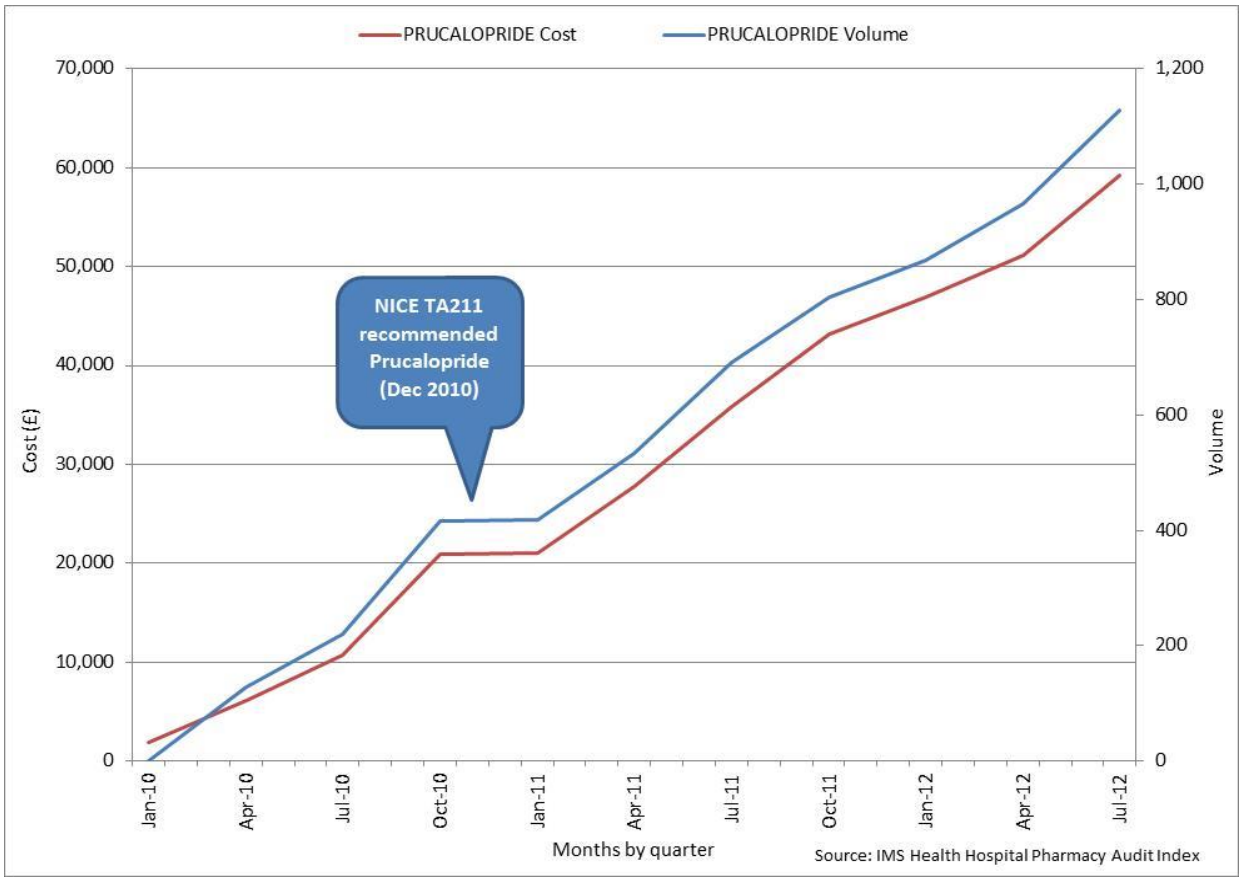
Figure 1 Cost and volume of Prucalopride prescribed in primary care and in hospitals that has been dispensed in the community in England.



1.2. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost and volume of Prucalopride prescribed and dispensed in hospitals in England between January 2010 and October 2012.

Figure 2 Cost and volume of Prucalopride prescribed and dispensed in hospitals in England



2. Implementation studies from published literature

Information is taken from the uptake database website.

Nothing specific to add.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing specific to add.

Addendum: Healthcare activity data definitions

ePACT

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions written in hospitals but dispensed in the community (FP10 [HP]) are not included in PACT data. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.