SUMMARY OF APPRAISAL COMMITTEE'S KEY CONCLUSIONS

FURTHER SUPPORTIVE EVIDENCE

[redacted]

Current practice (4.2, 4.5)

The positive comments of the committee are noted. In addition to the points made regarding rectal irrigation and off license use of laxatives, I should also add that a small proportion of patients seek recourse from surgical intervention. The high cost of colonic excisional surgery (usually subtotal colectomy) in respect of morbidity and poor (highly variable) outcomes should be considered especially since outcomes in the UK and Europe are particularly poor in this respect [1-3]. I see several patients every year who have progressed to type II intestinal failure as a result of ill-informed surgery for constipation (the annual NHS cost of such patients individually runs into the £100,000s). Further, sacral nerve stimulation has been recently used to treat to this group of patients with high attendant costs (equipment alone circa £12,000 pp). Despite initial favourable results [4], the reality is that this treatment is beset with problems of placebo response during the temporary evaluation and poor results of permanent stimulation [3,5]. Permanent stoma formation (the final solution) is associated with ongoing lifelong costs (est. £35,000 pp per annum in appliances medical and nursing care) aside from issues of body image and physical complications such as hernia and prolapse [6]. It is thus highly desirable to prevent progression to surgery.

The technology (4.11)

I agree that a 6 month period for the *collective / cumulative* use of at least 2 laxatives is reasonable provided that this is the correct interpretation of the guidance. In reality most patients will usually have used several different laxatives, however it would prove almost impossible to determine if they had used 2 different laxatives for 6 months each (as could also be interpreted). Indeed, it is recommended by most specialists that laxatives are rotated because of tolerance problems every 3 months [7]. I think that it is important not to be too restrictive in this interpretation because of the additional issue of 'inadequate relief' which is the more important (see below).

Evidence for clinical effectiveness (uncertainties generated by the evidence 4.4)

I think that problems with the definition of 'inadequate relief' are almost impossible to overcome both in ideal trial conditions and clinical practice. The fact that a patient responds to some degree from laxatives does not mean that they receive a satisfactory outcome in terms of

symptoms or quality of life. For instance, I have numerous patients who take strong laxatives such as picolax (used normally for bowel prep) daily and often at undesirable doses to effect defaecation. The laxatives are effective in producing evacuation but only at a cost of abdominal pain, diarrhoea and dehydration (occasional admissions result from electrolyte imbalance; deaths due to hypokalaemia have also occurred). Similarly, the patient who is dependent on taking 5 different laxatives at different times of day may not be refractory to these laxatives in respect of treating their constipation but may be severely impaired in terms of quality of life.

Evidence for cost effectiveness (What are the key drivers of cost effectiveness 4.10)

I agree that the costs presented by the manufacturer in its economic model were probably conservative. The true cost of chronic constipation is probably vastly underestimated and has been only partially addressed by epidemiological surveys [8-10]. I illustrate this with an albeit non-evidence-based example of a young lady I saw only yesterday. This 22-year-old had been prescribed multiple laxatives including picolax for the past 10 years i.e. even as a child. She has been a prisoner of her home, unable to attend university and unable to seek employment. She has now been taking prucalopride for 2 months and is off all laxatives. I do not claim that she is completely cured but her abdominal pain and bloating are sufficiently reduced that she can work 2 days per week and now has a social life. She also no longer has the costs of anal irrigation, anti-depressants and psychotherapy. More importantly, she will not now be pressing for surgery (see above). I have several other patients like this only in the short period since prucalopride became available in the UK.

REFERENCES

1. Knowles CH, Scott SM, Lunniss PJ. Colectomy for slow transit constipation: a review. Ann Surg 1999; 230: 627-639.
2. Gladman MA, Knowles CH. Surgical treatment of patients with constipation and fecal incontinence. Gastro Clin North America 2008; 37: 605-25.
3. Knowles CH, Rosen H, Pescatori M, Rintala R. Surgical management of constipation. Neurogastro Motil 2009; 21 (suppl 2): 62-71.
4. Kamm MA, Dudding TC, Melenhorst J, Jarrett M, Wang Z, Buntzen S, Johansson C, Laurberg S, Rosen H, Vaizey CJ, Matzel K, Baeten C. Sacral nerve stimulation for intractable constipation. Gut 2010; 59: 333-40.
5. Vitton V, Roman S, Damon H, Barth X, Mion F. Sacral nerve stimulation and constipation: still a long way to go. Dis Colon Rectum 2009; 52: 752-3.
6. Nastro P, Knowles CH, McGrath A, Heyman B, Porrett TRC, Lunniss PJ. Complications of intestinal stomata. In press Br J Surg, July 2010.
7. Whitehead WE, di Lorenzo C, Leroi AM, Porrett T, Rao SS. Conservative and behavioural management of constipation. Neurogastroenterol Motil 2009;21 Suppl 2:55-61.

8. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology 2009; 136: 376–86.
9. Nyrop KA, Palsson OS, Levy RL et al. Costs of health care for irritable bowel syndrome, chronic constipation, functional diarrhoea and functional abdominal pain. Aliment Pharmacol Ther 2007; 26: 237–48.
10. Cook IJ, Talley NJ, Benninga MA, Rao SS, Scott SM. Chronic constipation: overview and challenges. Neurogastroenterol Motil 2009;21 Suppl 2:1-8.

CONFLICT OF INTEREST

I have received financial remuneration from Movetis to act as a clinical advisor in 2010.

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