Critique of ERG report on Prucalopride

GENERAL COMMENTS

Responding to the ERG provides a valuable opportunity to clarify a number of factual issues that may have been unclear in the original submission.

Some of the issues raised in the ERG report emphasize weaknesses in the evidence base this is acknowledged but cannot be rectified. For example the economic analysis would have benefitted from direct measurement of EQ-5D in the clinical trials of Prucalopride. The absence of such data meant alternative metrics had to be used to calculate QALY outcomes in a form acceptable to NICE. Fortunately quality of life data was captured using validated disease specific questionnaires PAC-SYM and PAC-QOL; the data captured from these questionnaires was converted into EQ-5D equivalents through a process of mapping. The mapping process is based on the established Brazier methodology and has been validated and peer reviewed by Professor John Brazier. This was discussed fully with NICE at the decision problem meeting on 18th February 2010, NICE did not object. Incorporation of resource use data in the clinical trials would have provided valuable evidence for assessing the wider cost savings available to the NHS arising from the use of Prucalopride. Although this data cannot be collected retrospectively, an audit of NHS HES data has been run which shows the substantial cost of ineffectively treated chronic constipation during the year 2008/09 in England. The number of patients who were referred into secondary care for day case and inpatient treatment with a primary diagnosis of constipation was equal to 86.19 patients per 100,000 of the population at a cost of £115,000 per 100,000 of the population totalling £57,744,474. (NHS HES data 2008/09). It is anticipated that the use of prucalopride will significantly reduce the number of day case and in-patient treatments for chronic constipation.

The ERG report over-simplifies the definition of laxative refractory to the ability of a laxative to induce a bowel movement. This is not an accurate interpretation, certain types of stimulant laxatives will induce bowel movements, but they do not address:

- The underlying distressing symptoms of chronic constipation.
- The unpredictable and unpleasant nature of the laxative induced bowel movement
- Considered by the patient of what is adequate relieve of their chronic constipation.

The ERG challenges the appropriateness of the clinical evidence produced by the pivotal trials. Their criticism is the inclusion in the trials of a small proportion of male patients and patients who reported being satisfied with laxative treatment. The economic model does not include data from males when it generates outputs, and it has a facility for filtering out the data prom patients who were satisfied with laxative treatment. Excluding these patients who are not covered by the licensed indication improves the cost effectiveness of prucalopride.

SPECIFIC ISSUES RAISED IN THE ERG REPORT

1. WEAKNESSES (P7)

ISSUE

It appears that many patients responded to the use of bisacodyl treatment during the trials. Therefore many patients did not appear to be laxative-refractory and so do not fall into the licensed indication.

RESPONSE

This issue concerns the appropriate definition of laxative refractory and adequate response. The fact that a laxative stimulates a bowel movement does not address the issue of adequate symptomatic relief, frequency of evacuation and tolerability of the laxative for the patient. The ERG have oversimplified the definition to that of the ability of a laxative to induce a bowel movement.

The licensed indication for Resolor (prucalopride) is for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. In this context laxatives must have first been used, and have failed to provide adequate relief from symptoms associated with chronic constipation as set out in Rome III diagnostic criteria: insufficient criteria for IBS, and presence of two or more of the following symptoms for at least three months with symptoms onset at least six months prior to diagnosis.

Straining during at least 25% of defecations;

- Lumpy or hard stools in at least 25% of defecations;
- Sensation of incomplete evacuation for at least 25% of defecations;
- Sensation of anorectal obstruction/blockage for at least 25% of defecations;
- Manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor);
- Fewer than 3 defecations per week.

If a female patient has tried laxatives but does not achieve adequate relief from symptoms beyond improved bowel movement frequency alone, she should be considered as being laxative refractory.

Regarding use of rescue medication, the selection of trial population was based on the patient's own opinion at the outset of the trial. Patients were questioned about adequate relief provided by their laxative used in the 6 months preceding the trial. Approximately 80% of patients reported that the laxatives used in the preceding 6 months did not provide adequate relief. Together with the fact that these patients had endured an average duration of constipation of 20 years, with a mean frequency of 0.5 spontaneous complete bowel movements per week suggests that these patients are laxative refractory. Therefore the conclusion of refractory has nothing to do with the use of laxatives during the trial.

During the trial the use of laxatives was restricted according to a 'rescue rule': patients were only allowed to use a laxative if they did not have a BM for 3 or more days. The use of laxative was therefore very limited in both the placebo treated patients as the prucalopride treated patients.

ISSUE

EQ-5D was not measured in the pivotal trials and no literature on EQ-5D results were available for chronic constipation. SF-36 was measured but this was not used in the economic modelling. Most of the SF-36 results for the pivotal trials showed no significant differences. A disease-specific quality of life measure was used instead (PAC-QOL) which was then converted to EQ-5D using a mapping equation. This mapping equation appears to have been specifically developed for Prucalopride.

RESPONSE

PAC-QOL is a robust disease specific quality of life assessment tool not a drug specific tool.
It is acknowledged that mapping disease specific measures onto EQ-5D is always a second best option to direct measurement of EQ-5D within the trial. However given that this option was unavailable and that no EQ-5D results were available for chronic constipation from the literature there was no alternative than to undertake a mapping analysis.
The SF-36 data generated in the trials was limited and hence would not have provided a robust mapping in comparison to the large volume of disease specific data that was generated in the trials. To ensure the most accurate linkage possible the mapping analysis undertaken was specifically focussed on the data generated by the Prucalopride trials. The

SF-36 data was therefore used in the modelling as the vital link between PAC-QOL data and EQ-5D.
A separate analysis was undertaken directly linking SF-36 results contained in the trial to EQ-5D data. This analysis shows similar EQ-5D benefits associated with Prucalopride when linked directly to the limited amount of SF-36 data available.

ISSUE

No account has been taken of adverse events.

RESPONSE

Adverse events have a negative effect on health related quality of life which is captured in the utility score, hence adverse events were accounted for. Prucalopride has a well researched AE profile with the majority of AEs being both mild to moderate and transient. The proportion of patients discontinuing due to AEs was low. There is no evidence that adverse events directly related to prucalopride will require additional use of NHS resource.

ISSUE

No explicit allowance was made for withdrawal from treatment at any time after 4 weeks.

RESPONSE

The average duration of chronic constipation in the prucalopride clinical trials was twenty years. The fact that Prucalopride can achieve normal (i.e. three or more SCBMs) bowel function in a large proportion of these patients within four weeks emphasises the immediate clinical efficacy of Prucalopride. Data shows that patients who have responded inside four weeks will continue to benefit from treatment long-term with a very low drop out rate. The fact that patients who will not benefit from treatment with prucalopride can be identified inside the first four weeks means that treatment with prucalopride can be stopped after the initial 28 days. This allows targeting the use of prucalopride on patients who respond to treatment and this has been demonstrated to be cost effective.

AREAS OF UNCERTAINTY (P8)

ISSUE

Since trials were not conducted in the appropriate type of patients, it is uncertain how effective Prucalopride is in the patient group for which it is licensed: women who are refractory to laxatives.

RESPONSE

The licensed indication for prucalopride being reviewed in this appraisal is for the symptomatic treatment of chronic constipation in women in whom standard laxatives fail to provide adequate relief. The inclusion and exclusion criteria for the trials ensured that patients recruited to the trials had a diagnosis of chronic constipation and had previously received treatment for their condition. Therefore appropriate patients were recruited and we can be certain of the effectiveness of prucalopride.

The Economic modelling undertaken for both adults and elderly patients is using data entirely from female patients with chronic constipation. The economic model provides a filter facility to run an analysis of female patients who are laxative refractory. This group of patients shows an improved cost effectiveness when compared to the total population.

ISSUE

It is uncertain how effective Prucalopride is compared to the other comparators specified in the NICE scope decision problem, i.e. invasive procedures and bowel surgery.

RESPONSE

Invasive procedures and bowel surgery are not appropriate comparators as these are infrequently used and are reserved as rescue treatments (this point was discussed and resolved with the NICE technical team on 18th February 2010). Prucalopride is indicated for use prior to initiating such costly invasive therapies. The majority of such rescue treatments provide short term relief at high cost, the NHS in England 2008/09 spent over £33,400,000 on 23,000 interventions for females. None of these procedures have been assessed for cost effectiveness by NICE.

ISSUE

The relative long-term effectiveness of Prucalopride compared to placebo is uncertain. The effectiveness results suggested a small comparative reduction in effectiveness between 4 and 12 weeks. High rates of patient drop-out from extension studies were likely to give an optimistic estimate of long-term effectiveness. Extension studies were only in patients given Prucalopride (and not placebo) so no comparative evidence is available beyond 12 weeks.

RESPONSE

A paper discussing the long-term open label extension of the pivotal studies has been accepted for publication in Alimentary Pharmacology and Therapeutics, the lead author is Camilleri M. Clinical trial: efficacy of open-label prucalopride treatment in patients with chronic constipation – combined results of three trials, content from this paper is subject to academic confidentiality

AIC information removed
The long term data emphasises that patient satisfaction (as measured with the PAC-QOL satisfaction subscale), stabilizes in the first year of treatment in adult patients and slightly increases in elderly patients. The open label long term extension was focused on tolerability and safety, efficacy was a secondary consideration. However the evidence as measured by patient satisfaction shows that efficacy does not diminish with time.

The reason that patients recorded a slight drop in satisfaction from week 4 to week twelve is due to the physical nature of chronic constipation. The mean duration patients endured chronic constipation in the trials was 20 years, the effect of prucalopride in these patients is to clear a backlog from their bowels during the initial period, the symptomatic relief brought about by this change reduces as bowel motility and frequency of defecation return to normal. Therefore a slight reduction between weeks 4 and 12 is confirmation of the mechanism of action. It is correct that no comparative evidence is available beyond twelve weeks, for methodological and ethical reasons it was inappropriate to continue with patients on placebo as the objective of the extension study was tolerability and safety.

ISSUE

No meta-analysis of trial results was conducted, yet “pooling of clinical data” was conducted for the economic modelling. It is uncertain how this was done.

RESPONSE

The design of the three pivotal trials was identical enabling the pooling of data. Data from other trials of similar design with appropriate endpoints and objectives were also available and were used for the purposes of modelling.

ISSUE

It is uncertain how the differences in trial populations compared to the scope of the appraisal would affect cost-effectiveness. However, if 20% of participants in the pivotal trials had not previously used laxatives, they would be more likely to respond to any treatment, compared to those who had tried a number of previous laxatives. Therefore, the effectiveness would appear to be greater, which would improve the cost effectiveness.

RESPONSE

Although counter-intuitive, including patients who are laxative naïve increases the cost per qaly gained. A separate analysis was undertaken excluding these patients and the impact on the overall cost effectiveness of Prucalopride improved. This is due to the fact that treatment naive patients have less severe chronic constipation so consequently their health gain is lower. The base case for adult females including a small proportion of laxative naïve gave a cost per qaly of £16600, compared to £15100 when the laxative naïve patients were excluded, similarly including a small proportion of laxative naïve patients in the elderly group gave a base case of £14,000 compared to £11,100 when this group were excluded.

ISSUE

It is unclear how using the SF-36 results would have affected the cost effectiveness estimates. As there were mostly no significant differences in SF-36 results for the pivotal trials, it is possible that the calculated cost effectiveness results would have been higher.

RESPONSE

The limited SF-36 data available was used to facilitate mapping of the far more extensive PAC-QOL data to EQ-5D.

A separate analysis was undertaken to test the impact of directly linking the SF-36 data to EQ-5D using the Brazier algorithm. These calculated outcomes are comparable to those calculated in the mapping exercise.

ISSUE

The clinical effectiveness results actually used in the economic modelling are unclear, as several of the studies used in the model (INT-1, INT-2, USA-3, GBR-4, FRA-1, USA-26) are not fully described in the submission.

RESPONSE

CSRs were provided to NICE for INT1, INT2 USA3 USA 26 with the original submission.
All appropriate data was used to inform the clinical model. Trials concerning the use of Prucalopride in specific subset diseases were excluded as the analysis wanted to evaluate the cost effectiveness in the general population.

Only data from elderly female patients using 1mgof prucalopride was included for the economic modelling of 1mg cost effectiveness. There was insufficient data on these 1mg dose elderly patients from the pivotal studies to drive this sub-group in the economic model. For this reason data from a dose ranging and a safety trial were included, the limitation of this data was the 4week duration of the trial, the data from these patients had to be extrapolated for the 12 and 52 week endpoints. To ensure appropriateness the extrapolated outcomes were derived from elderly female patients outcomes using 1mg dose.

ISSUE

The assumption that the last measured QALY gain is sustained for the rest of the year is not tested in the model.

RESPONSE

This assumption is based on the results obtained from the long term observational trial data. The self selecting nature of such data is well known. However if patients withdraw from therapy due to reduced efficacy their costs are also negated. The available evidence emphasises the sustained efficacy of Prucalopride in patients who remain on therapy.

2. KEY ISSUES (P9)

ISSUE

It is likely that the effectiveness of Prucalopride has been overestimated, due to issues to do with patient selection, comparator used, outcomes used or not used and extension study issues in the trials and studies where this information was made available.

RESPONSE

The effectiveness of Prucalopride has been extensively evaluated in a large number of high quality clinical trials. The quality and quantity of evidence generated in these trials emphasises the clinical value of Prucalopride in treating chronic constipation quickly and effectively in patients with long term experience of this disease.

Issues of patient selection appear to centre around a comparatively few patients who appear to have been included in the trials despite having no prior recorded use of laxatives. Rerunning the economic model excluding this small number of patients improves the measured cost effectiveness of Prucalopride.

Rescue laxatives such as bisocodyl cause a patient to evacuate their bowel; this is frequently an unpredictable and unpleasant experience for the patient. This type of laxative does not adequately treat the symptoms of chronic constipation but may help avoid faecal impaction in these patients.

ISSUE

There are unsubstantiated assumptions relating to the long-term (52 weeks) effectiveness of Prucalopride.

RESPONSE

The evidence obtained from the long term trials is neither unsubstantiated or assumption based. Whilst recognising that observational data is of lower evidential quality than clinical trial data the available evidence emphasises the sustained impact of Prucalopride in the (admittedly self selected) patient group being supported over the first 12 months of treatment by Prucalopride.

ISSUE

There is a lack of transparency around patients and trial and study results used to inform the economic model

RESPONSE

The analysis was specifically undertaken at individual patient level to maximise the flexibility and transparency of the analysis undertaken. All relevant clinical trial data has been used to inform the economic analysis and all data is available for audit as required.

ISSUE

The data used for mapping effectiveness to EQ-5D was not made available.

RESPONSE

All data utilised in the mapping analyses are available for peer review. All analyses are available for replication as required to ensure the robustness and rigour of the analyses undertaken. The structure of the mapping analysis has been subject to both internal and external review and a paper has been accepted for publication in a peer reviewed journal (Pharmacoeconomics) that specifically outlines the methodology and results obtained in this analysis. A copy of the final version of the submitted paper is available on request.

ISSUE

If the regression results are to be believed, it is possible that Prucalopride is cost-effective. However, the lack of transparency in the results from the 10 Prucalopride trials and studies feeding into the economic model and the lack of transparency over the EQ-5D mapping means that it is not possible to establish a more accurate estimate of cost effectiveness.

RESPONSE

Every attempt has been made to make the economic case for Prucalopride evidence based. The need to avoid basing this submission on assumptions made in the absence of evidence has frequently led to the analysis avoiding areas where significant advantages would appear to arise from the use of Prucalopride. In particular it would appear that extensive use is made of primary care consultations by revolving door patients whose failure to identify a satisfactory resolution to their long term chronic constipation has led to extensive use of expensive diagnostic and invasive procedures all of which only provide a temporary solution to the problem. Issues relating to the apparent lack of transparency have been dealt with elsewhere but the economic methodology underlying the mapping has been subject to extensive peer review.

As such there is every reason to believe the regression results which implies that on any reasonable assumption Prucalopride should be interpreted as being cost effective in relation to thresholds normally used to guide decision making with regard to cost effectiveness.

3. SUMMARY OF COST EFFECTIVENESS ISSUES (P75)

The main limitations of the analysis are as follows:

The first three of these issues have been addressed through additional work undertaken by the ERG.

ISSUE

It has not been possible to verify the regression equations used to determine the treatment effects in the model. This includes both the clinical effectiveness and the mapping of patient outcomes to EQ-5D.

RESPONSE

Addressed through additional work undertaken by ERG.

ISSUE

No account has been taken of adverse events.

RESPONSE

Addressed through additional work undertaken by ERG.

ISSUE

Some results were only given in terms of the overall population. It is important to separate the two age groups: adult and elderly.

RESPONSE

Addressed through additional work undertaken by ERG.

ISSUE

The model only allowed for variation in the response rate and mean treatment rates to be addressed through the “compliance” figure. Uncertainty in this figure was not included in the probabilistic analysis.

RESPONSE

Uncertainty in compliance (a mixture of compliance amongst responders and cost of non-responders) was not included in PSA given the lack of any evidence on which to base such changes. The figure used was therefore based on a highly conservative point estimate.

ISSUE

No explicit allowance was made for withdrawal from treatment at any time after 4 weeks.

RESPONSE

Withdrawal from treatment at any time leads to a cessation of both costs and benefits arising to the individual patient. In this manner no alteration in the overall cost effectiveness ratio for Prucalopride would arise.

ISSUE

The assumption that the last measured QALY gain is sustained for the rest of the year is not tested in the model.

RESPONSE

The data available from the long term trials shows that the average levels of satisfaction experienced by patients treated with Prucalopride actually increases over the first year of treatment. Part of this increase results from the long term self selection which ensures that continued use of Prucalopride is targeted on patients who obtain the greatest benefit from this therapy. Thus in comparison to the evidence the assumption that treatment efficacy is merely maintained appears conservative.