naloxegol 12.5mg and 25mg film-coated tablets (Moventig®) SMC No. (1106/15)
AstraZeneca UK Ltd

06 November 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

naloxegol (Moventig®) is accepted for use within NHS Scotland.

**Indication under review**: the treatment of opioid-induced constipation in adult patients who have had an inadequate response to laxative(s).

Naloxegol compared to placebo significantly improved the response rate in patients with opioid-induced constipation including patients who had previously had an inadequate response to at least four days of treatment with at least one class of laxative.

Overleaf is the detailed advice on this product.

Vice-Chairman,
Scottish Medicines Consortium

Published 07 December 2015
**Indication**
For the treatment of opioid-induced constipation in adult patients who have had an inadequate response to laxative(s). An inadequate response was defined as having opioid-induced constipation symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the previous two weeks.

**Dosing Information**
Naloxegol 25mg orally once daily. It is recommended that naloxegol is taken in the morning, for patient convenience to avoid bowel movements in the middle of the night. Naloxegol should be taken on an empty stomach at least 30 minutes prior to the first meal of the day or two hours after the first meal of the day. When naloxegol is initiated, it is recommended that all currently used maintenance laxative therapy should be halted until the clinical effect of naloxegol is determined.

In patients with moderate or severe renal insufficiency or in patients taking moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil), the recommended starting dose is 12.5mg once daily which, if well tolerated, can be increased to 25mg once daily.

**Product availability date**
September 2015

**Summary of evidence on comparative efficacy**

Naloxegol is a pegylated derivative of the opioid antagonist naloxone. It acts as a peripherally-acting mu-opioid receptor antagonist in the gastro-intestinal tract, decreasing the constipating effects of opioids without impacting on opioid-mediated analgesic effects on the central nervous system.¹

The key evidence to support the use of naloxegol in opioid-induced constipation comes from two identical, double-blind, randomised, phase III studies (KODIAC 4 and 5).²³ Eligible patients were aged 18 to 84 years and had been taking a stable dose of oral opioid (30mg to 1000mg of morphine or equivalent) for non-cancer pain for at least four weeks. They had self-reported opioid-induced constipation (defined as less than three spontaneous bowel movements [SBM] per week plus at least one of the following symptoms in at least 25% of bowel movements during the four weeks before screening: hard or lumpy stools, straining or a sensation of incomplete evacuation or anorectal obstruction) which was confirmed during a two-week run-in period. At least 50% of patients enrolled to the studies had an inadequate response to laxatives (defined as taking medicine from at least one laxative class for at least four days within the two weeks before screening and with symptoms rated as moderate, severe or very severe in at least one of the four stool-symptom domains of the laxative-response questionnaire at baseline). Patients were randomised equally to receive naloxegol 25mg, naloxegol 12.5mg or placebo orally once daily for 12 weeks with stratification by laxative-response status at pre-screening. During the screening and treatment periods, the use of laxatives, bowel-
treatment regimens, opioid antagonists, mixed antagonists and strong inhibitors of cytochrome P450 3A4 and P-glycoprotein were not permitted. If a bowel movement had not occurred in 72 hours, rescue medication with up to three doses of bisacodyl (10 to 15mg orally per episode) plus, if required, one enema, was allowed.\textsuperscript{2,3}

In both studies, the primary outcome was the response rate during the 12-week treatment period, defined as at least three SBM (bowel movement without use of rescue laxative medication) per week and an increase of at least one SBM from baseline for at least nine weeks of the 12-week treatment period and at least three weeks in the last four-week treatment period. In the intention to treat (ITT) population, response rates were 44\% (95/214) in the naloxegol 25mg group, 41\% (87/213) in the naloxegol 12.5mg group and 29\% (63/214) in the placebo group in KODIAC 4 and 40\% (92/232) in the naloxegol 25mg group, 35\% (81/232) in the naloxegol 12.5mg group and 29\% (68/232) in the placebo group in KODIAC 5. Response rates were significantly higher in both naloxegol groups compared with placebo in KODIAC 4 but only in the naloxegol 25mg group compared with placebo in KODIAC 5.\textsuperscript{2,3}

The key secondary outcome was response rate during 12 weeks in the laxative inadequate responder subgroups of each study. This subgroup reflects the licensed population. Details of results are presented in table 1. The studies used multiple fixed sequence testing, and since the naloxegol 12.5mg dose was not statistically significantly better than placebo in the primary outcome in the ITT population of KODIAC 5, further statistical significance cannot be claimed for analysis of subsequent outcomes in naloxegol 12.5mg versus placebo in this study.

**Table 1**: Response rates in laxative inadequate responder subgroups of KODIAC 4 and 5 (licensed population)\textsuperscript{1,2,3}

<table>
<thead>
<tr>
<th></th>
<th>KODIAC 4</th>
<th>KODIAC 5</th>
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<tr>
<td></td>
<td>Naloxegol 25mg</td>
<td>Naloxegol 12.5mg</td>
</tr>
<tr>
<td>Laxative inadequate responder subgroup</td>
<td>n=117</td>
<td>n=115</td>
</tr>
<tr>
<td>Response rate (%) (n/N)</td>
<td>49% (57/117)</td>
<td>43% (49/115)</td>
</tr>
<tr>
<td>Relative risk versus placebo (95% CI) p-value</td>
<td>1.69 (1.21 to 2.37) (p=0.002)</td>
<td>1.50 (1.04 to 2.11) (p=0.028)</td>
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</table>

CI: confidence interval
* according to the multiple fixed sequence testing, results of further statistical analysis is not appropriate
Results of other secondary outcomes included time to first post-dose SBM, number of days per week with at least one SBM and mean change from baseline in number of SBM per week. These outcomes significantly favoured naloxegol 25mg compared with placebo in the ITT and laxative inadequate responder subgroup (licensed population). The severity of straining (measured on a scale from 1=not at all to 5=an extreme amount) was significantly more improved in the naloxegol 25mg versus placebo group in the ITT populations and laxative inadequate responder subgroups of both studies. Stool consistency was assessed using the Bristol stool scale (1 to 7) and was also significantly more improved in the naloxegol 25mg group versus placebo in the ITT populations and laxative inadequate responder subgroups of both studies.

Results from a pooled analysis of KODIAC 4 and 5 in a subgroup of patients who had inadequate response to at least two classes of laxatives during previous opioid treatment found that response rates over 12 weeks were higher in the naloxegol groups compared with placebo: 44% (44/99) in the naloxegol 25mg group, 44% (39/88) in the naloxegol 12.5mg group and 30% (27/90) in the placebo group (p=0.04 and p=0.05 for naloxegol 25mg and 12.5mg respectively versus placebo). Quality of life was measured using the patient’s assessment of constipation symptoms (PAC-SYM) and the patient’s assessment of constipation quality of life (PAC-QoL). In the laxative inadequate responder subgroup, naloxegol 25mg and 12.5mg resulted in significantly greater improvements from baseline to week 12 compared with placebo in PAC-SYM total scores in both studies. Naloxegol 25mg was also associated with significantly greater improvements from baseline to week 12 compared with placebo in PAC-SYM rectal and stool domain scores in both studies. However, there was no significant difference for naloxegol over placebo in the abdominals symptoms score. There were improvements in the PAC-QoL total and all domain scores during the 12-week treatment period in all groups in the ITT populations of both studies but there were no significant differences between groups, except in the satisfaction domain in KODIAC 5.

The KODIAC 6 study was designed to assess the efficacy and safety of naloxegol in patients with opioid-induced constipation and cancer-related pain. However, due to problems with recruitment, the study was terminated early after only 14 patients were enrolled.

### Summary of evidence on comparative safety

In the overall study populations of the KODIAC 4 and 5 studies respectively, adverse events were reported in 61% (131/214) and 69% (160/232) of the naloxegol 25mg groups, 49% (104/211) and 60% (137/230) of the naloxegol 12.5mg groups and 47% (100/213) and 59% (136/231) of the placebo groups. Adverse events were considered serious in 3.3% and 3.4% of naloxegol 25mg groups, 5.2% and 6.1% of naloxegol 12.5mg groups and 5.2% and 5.2% of placebo groups respectively and led to discontinuation in 10% and 10%, 4.3% and 5.2%, 5.6% and 5.2% of patients respectively. Discontinuation due to adverse events was higher in the naloxegol 25mg groups of both studies and this was mainly due to gastro-intestinal adverse events.

In the overall study population of KODIAC 4, the most frequently reported adverse events in the naloxegol 25mg, naloxegol 12.5mg and placebo groups respectively were abdominal pain (13%, 8.5% and 3.3%), diarrhoea (9.3%, 3.3% and 4.3%), nausea (7.5%, 7.1% and 4.7%), flatulence (5.6%, 4.3% and 1.9%) and upper abdominal pain (5.1%, 1.4% and 1.9%). In the overall study population of KODIAC 5, the most frequently reported adverse events in the naloxegol 25mg, naloxegol 12.5mg and placebo groups respectively were abdominal pain (19%, 11% and 7.8%), diarrhoea (9.1%, 7.8% and 4.3%), nausea (8.6%, 6.1% and 4.3%), vomiting (6.0%, 3.0% and 2.6%), flatulence (6.0%, 1.7% and 3.0%), headache (5.2%, 5.2% and 3.5%) and back pain (5.2%, 5.2% and 1.7%).
Pooled analysis of KODIAC 4 and 5 indicated that the overall incidence of adverse events was similar in the laxative inadequate responder and non-laxative inadequate responder subgroups: 63% (152/241) in the naloxegol 25mg group, 51% (120/237) in the naloxegol 12.5mg group and 50% (119/238) in the placebo group of the pooled laxative inadequate responder subgroups compared with 64% (131/205), 54% (111/204) and 52% (108/206) respectively in the pooled non-laxative inadequate responder subgroups.\(^3\)

A randomised, double-blind, 12-week extension to the KODIAC 4 study, designed to assess the safety and tolerability of naloxegol 25mg daily, 12.5mg daily or placebo for up to six months (KODIAC 7), found an incidence of adverse events in 41% (40/97) of naloxegol 25mg patients, 34% (32/94) of naloxegol 12.5mg patients and 33% (33/100) of placebo patients. Serious adverse events were reported in 6.2% (6/97), 6.4% (6/94) and 5.0% (5/100) of patients respectively and adverse events led to discontinuation in 4.1% (4/97), 4.3% (4/94) and 3.0% (3/100) of patients respectively.\(^3,4\)

KODIAC 8 was a 52-week, open-label extension study to assess the longer term safety of naloxegol which enrolled 804 patients, including new patients and patients from KODIAC 5 and the extension to KODIAC 4. Patients were randomised to receive naloxegol 25mg daily (n=534) or usual care (n=270) for 52 weeks. Treatment-emergent adverse events were reported in 82% of naloxegol and 72% of usual care patients. Serious adverse events were reported in 9.6% and 11% of patients respectively and adverse events led to discontinuation in 11% of naloxegol patients (data not available for usual care patients).\(^5\)

### Summary of clinical effectiveness issues

Naloxegol is a pegylated derivative of the opioid antagonist naloxone. Methylnaltrexone is another peripheral opioid antagonist, originally licensed for the treatment of opioid-induced constipation in advanced illness in adult patients receiving palliative care when response to laxative therapy had not been sufficient. This indication was reviewed by SMC in 2008 and restricted further to use by physicians with expertise in palliative care. The marketing authorisation for methylnaltrexone was recently widened to treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients.\(^6\) This wider indication has not yet been reviewed by SMC.

Evidence to support the use of naloxegol in the licensed population (i.e. patients with opioid-induced constipation who have had an inadequate response to laxative[s]), comes from subgroup analyses of the two pivotal studies. The studies were designed and powered for such analyses, however, as noted above, since naloxegol 12.5mg was not significantly better than placebo in the primary outcome in the ITT population of KODIAC 5, further statistical significance could not be claimed for analysis of subsequent outcomes in naloxegol 12.5mg versus placebo in this study. There was a statistically significant increased response rate with naloxegol 25mg than placebo and the difference, although smaller than expected, met a clinically relevant difference of 10%. The treatment effect was larger in the subgroup who had an inadequate response to laxative(s) than those who had not.\(^2,3\)

Controlled data from the two pivotal studies are limited to 12 weeks duration but are confirmed in extension studies to 52 weeks.\(^2,3,5\)

The pivotal studies did not include patients with opioid-induced constipation and cancer pain. One study was designed to assess the efficacy and safety of naloxegol in patients with opioid-induced constipation and cancer-related pain but was terminated early due to recruitment problems. However there appears to be no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in this patient population and this was considered acceptable by the European Medicines Agency.\(^2\) The summary of product characteristics (SPC) notes that there is limited clinical experience
with the use of naloxegol in opioid-induced constipation patients with cancer-related pain. Therefore, caution should be used when prescribing naloxegol to such patients. The SPC also notes that naloxegol is contra-indicated in patients with underlying cancer who are at heightened risk of gastro-intestinal perforation including those with underlying malignancies of the gastro-intestinal tract or peritoneum, recurrent or advanced ovarian cancer or receiving vascular endothelial growth factor (VEGF) inhibitor treatment.¹

Patients at increased risk of gastro-intestinal perforation or with a recent history of myocardial infarction (previous six months), symptomatic congestive heart failure, overt cardiovascular disease or patients with a QT interval ≥500msec were excluded from the KODIAC 4 and 5 studies and therefore the impact of naloxegol on these patients is unknown.¹,⁵

There are no comparative data versus other laxatives and the company represented a Bucher indirect comparison with methylnaltrexone in patients with opioid-induced constipation and non-cancer related pain to support a scenario analysis in the economic case. This included four studies: the two pivotal naloxegol studies (using laxative inadequate responder subgroups) and two methylnaltrexone studies (one using licensed subcutaneous methylnaltrexone). Outcomes compared were mean change in SBM per week and SBM response (defined as the proportion of patients with ≥ three SBM per week over a four-week treatment period). The results suggested that the mean change in SBM per week was significantly greater with naloxegol 25mg compared with methylnaltrexone 12mg given subcutaneously on alternate days but not different from methylnaltrexone 12mg given subcutaneously daily and was significantly less with naloxegol 12.5mg compared methylnaltrexone 12mg given subcutaneously daily. There were no significant differences between naloxegol 25mg or 12.5mg and methylnaltrexone in SBM response. However, there are a number of limitations which may affect the validity of the results including differences in populations, limited data from the methylnaltrexone studies to allow comparison of the populations and a shorter four-week duration in the methylnaltrexone subcutaneous study.

The introduction of naloxegol would offer an oral medicine for the management of opioid-induced constipation in patients who have had an inadequate response to laxative(s). The SPC for naloxegol defines an inadequate laxative response as opioid-induced constipation symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the previous two weeks. Clinical experts consulted by SMC suggested that there is no standard definition of laxative inadequate response but in practice they consider this to be patients that had not responded to more than one laxative, confirmed over a longer period of time.

### Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis which compared naloxegol 25mg against no treatment for the treatment of opioid induced constipation (OIC) in adult patients who have had an inadequate response to laxatives.

The company used a decision analytic model to assess the cost-effectiveness of naloxegol versus the comparator. The model consisted of a decision tree structure for the first four weeks of treatment, followed by a Markov model with a time horizon of five years. Patients started the analysis in the decision tree component of the model and received naloxegol or the comparator medicine in order to treat their OIC. Response to treatment was assessed after four weeks and patients were classified as responders if they had achieved constipation relief over four weeks and as non-responders if they had not. The Markov model consisted of four health states: OIC, non-OIC (on-treatment), non-OIC (untreated) and death. Patients who were in the OIC state did not receive treatment and could transition to the non-OIC (untreated) state, while patients in the non-OIC (untreated) state could...
transition to the OIC health state. Patients who were in the non-OIC (on treatment) health state could transition to the OIC health state where they were no longer on treatment. Patients could also remain in their health state or transition to death.

The source of the clinical data used in the economics was primarily the KODIAC 4 and KODIAC 5 studies. These data informed the proportion of patients in the non-OIC (on treatment) health state at week 4 as well as the transition probabilities in the base case Markov model. Data from an indirect comparison were used for a comparison of naloxegol versus subcutaneous methylnaltrexone which was provided as a scenario analysis.

Utility estimates were taken from the KODIAC 4 and 5 studies which collected EQ-5D data. The utility inputs were treatment specific and also time dependent as different utility values were applied to the non-OIC (on treatment) health state for patients initiated to naloxegol for cycles 1 and 2 of the model versus cycle 3 onwards.

Medicines costs were included in the analysis as were costs related to constipation associated Health Care Resource Use (HCRU). The HCRU costs included inpatient hospitalisation, outpatient and emergency department visits, primary care consultations and imaging and laboratory tests.

The base result indicated that the incremental cost-effectiveness ratio (ICER) for naloxegol versus no treatment was £11,021 per quality adjusted life year (QALY) gained. This result was based on an incremental cost for naloxegol versus no treatment of £260 and an incremental QALY gain of 0.024. The economic model was most sensitive to using health state specific utility values (trial data) (£39,540), decreasing the utility in the non-OIC (untreated) states in cycle 3 onwards of all comparators by 20% (£36,190), decreasing the intercept parameter for naloxegol by 20% (£29,998), increasing the utility in non-OIC (on treatment) state in cycles 3 onwards in the no treatment arm by 20% (£27,883) and reducing the time horizon to 12 weeks (£26,620). When the utility in the non-OIC (on treatment) state in cycles 3 and onwards for naloxegol was reduced by 20% naloxegol was dominated (i.e. more costly and less effective) by no treatment.

The company stated that the base case analysis was naloxegol versus no treatment since placebo was the comparator in the pivotal clinical studies. However the company also suggested that the most clinically relevant comparisons were naloxegol versus bisacodyl and naloxegol plus bisacodyl versus bisacodyl. For the comparison of naloxegol versus bisacodyl the ICER was £12,762. This result was based on an incremental cost of £275 and QALY gain of 0.022 QALYs. For the comparison of naloxegol plus bisacodyl versus bisacodyl the ICER was £11,327. This result was based on an incremental cost of £317 and QALY gain of 0.028 QALYs.

A scenario analysis was also provided which compared naloxegol versus methylnaltrexone. The result suggested that naloxegol was dominant (i.e. was less costly and more effective) versus methylnaltrexone.

The base case analysis used clinical data primarily from the KODIAC 4 and 5 studies which did not include patients with OIC and cancer pain. The company also provided a scenario analysis based on cancer pain patients which increased the age and mortality estimates of the population included in the base case analysis. This scenario generated an ICER of £10,999 for naloxegol versus placebo.

The main weaknesses of the analysis were:

- Some SMC clinical experts have suggested methylnaltrexone may be the treatment that is displaced, but the recent licence extension for methylnaltrexone has not been assessed by SMC. In addition, the relative efficacy of naloxegol versus methylnaltrexone was derived from an indirect comparison which was associated with a number of limitations. It is also not clear if this analysis includes non-significant differences in efficacy. While the comparator was
uncertain, the range of analyses provided by the company was considered to be appropriate.

- The analysis used treatment and time specific utilities which reported a utility increment for naloxegol versus placebo. A scenario analysis provided by the company which used health state specific utility values increased the ICER to £39,540. It is also worth noting that when placebo plus bisacodyl was included as the comparator the ICER increased to £64,041. However, given the EQ-5D data were collected in the study the additional benefit with naloxegol may reflect patients experiencing a better response to treatment and therefore the non-OIC health state may be too broad. Additional data were provided by the company which showed patients who responded on naloxegol appeared to have a better response and therefore the quality of life data used in the base case analysis was considered to be appropriate.

- The cycle length used in the analysis was four weeks which may have overestimated the disutility patients may feel if classified as a non-responder. This was because during that four week period patients could have more than 3 SBMs in at least one of the last four weeks and still be classified as being in the OIC health state. The company response suggested that a four week cycle length did not bias utility estimates in favour or against a health state. This was because within this time period a patient deemed non OIC may have a week where they experience <3 SBMs, however conversely a patient who is deemed OIC can have up to 2 weeks experiencing ≥3 SBMs. Therefore it was difficult to determine the direction of the bias (if any) the cycle length in the model may have generated.

- The company estimated the longer term efficacy of the comparators using extrapolation of the clinical study data. The extrapolation included estimating the exponential, Weibull, log-logistic and log-normal functions and the sensitivity analysis provided by the company did not highlight that the choice of curve had a material impact on the base case ICER. However the Gamma and Gompertz curve were also available for estimation and from visual inspection the Gamma curve was the most conservative for naloxegol. The SMC Statistical Advisor noted that the AIC values for each curve were similar so it was difficult to identify one particular curve which was the most appropriate. The SMC Statistical Advisor also highlighted that the log-normal curve had the lowest AIC for both treatments. When the log-normal curve was used in the analysis the ICER was £8,990.

Despite these limitations, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The Scottish Palliative Care Guidelines on constipation in palliative care were issued in May 2014 and last updated in May 2015. The guidelines do not specifically provide treatment outlines for opioid-induced constipation but opioid use is mentioned as a possible cause of constipation. A number of treatment options are recommended which may be equally effective and patient preference may be considered. These include a stimulant ±softener (e.g. senna or bisacodyl at bedtime and if stools become hard or colic supervenes then a softening agent can be added e.g. docusate sodium); osmotic laxative (e.g. macrogol); combined stimulant and softener licensed for terminally ill patients (e.g. co-danthramer); rectal preparations and treatments for paraplegic or bedbound patients. The guidelines state that methylnaltrexone may be suitable for opioid-induced constipation that is resistant to standard therapies.
Additional information: comparators

No relevant comparators in this treatment setting.

Cost of relevant comparator

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
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<tbody>
<tr>
<td>Naloxegol</td>
<td>12.5 to 25mg orally once daily</td>
<td>670</td>
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</table>

Cost from eVadis August 2015.

Additional information: budget impact

The company estimated there were 25,460 patients eligible for treatment in year 1 rising to 26,435 in year 5. Treatment uptake was estimated at 5% in year 1 and rising to 15% in year 5. This resulted in 1,146 patients assumed to be treated in year 1 rising to 3,569 in year 5 once discontinuation of 10% had been taken into account.

The gross medicines impact was estimated as £769k in year 1 rising to £2.4m in year 5. As medicines were assumed to be displaced the net medicines budget impact was estimated as £576k in year 1 rising to £1.8m in year 5.
References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. AstraZeneca Uk Ltd. Summary of product characteristics, naloxegol (Moventig®) 12.5mg and 25mg tablets. 25 June 2015.


4. NCT01395524 A 12-week extension of the phase III study (D3820C00004) to assess the effect and safety of NKTR-118 in patients with non-cancer-related pain and opioid-induced constipation www.clinicaltrials.gov [accessed 31 August 2015].


6. TMC Pharma Services Ltd. Summary of product characteristics, methylnaltrexone (Relistor®) 12mg/0.6ml solution for injection, 22 July 2015.


This assessment is based on data submitted by the applicant company up to and including 16 October, 2015.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.