Retigabine for the adjunctive treatment of partial onset seizures in epilepsy

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1 Guidance

1.1 Retigabine is recommended as an option for the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate has not provided an adequate response, or has not been tolerated.
2 The technology

2.1 Retigabine (Trobalt, GlaxoSmithKline) reduces neuronal activity by opening potassium channels found in neuronal cells. This stabilises the resting membrane potential and controls the electrical excitability in neurons. This mechanism of action is thought to be how retigabine prevents epileptic seizures. Retigabine has a marketing authorisation ‘as adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy’.

2.2 The summary of product characteristics suggests caution when prescribing retigabine with medicinal products known to increase the QT interval and in patients with a known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia, and in patients who are aged 65 years and older when starting treatment. In these patients, the summary of product characteristics recommends that an electrocardiogram (ECG) is recorded before starting treatment with retigabine, and in those with a corrected QT interval of greater than 440 ms at baseline, an ECG should be recorded on reaching the maintenance dose.

2.3 Retigabine is taken orally. The maximum total daily starting dose is 300 mg (100 mg three times daily). Thereafter, the total daily dose is increased by a maximum of 150 mg every week, according to the patient's response and tolerability, to between 600 mg/day and 1200 mg/day. The maximum maintenance dose is 1200 mg/day. For patients aged 65 years and older, the summary of product characteristics states that the total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week, according to the individual patient response and tolerability, up to a maximum maintenance dose of 900 mg/day.

2.4 Retigabine is available as 50-mg, 100-mg, 200-mg, 300-mg and 400-mg tablets. The 50-mg and 100-mg tablets are available in packs of 21 and 84. The other tablets are available in packs of 84 only. The price for a pack of 84 50-mg tablets is £19.46. The manufacturer calculates that the mean daily cost
of retigabine for the maintenance phase is £3.84. Costs may vary in different settings because of negotiated procurement discounts.
3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of retigabine and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer submitted evidence on the clinical effectiveness of retigabine from three randomised double-blind controlled trials, one phase IIb trial (study 205, N = 399) and two phase III trials (RESTORE 1, N = 306 and RESTORE 2, N = 539). Study 205 compared three doses of retigabine (600 mg, 900 mg and 1200 mg) with placebo. RESTORE 1 compared retigabine 1200 mg with placebo and RESTORE 2 compared retigabine 600 mg and 900 mg with placebo. People in the studies had an average age of approximately 37 years, with a history of epilepsy of approximately 22 years. The majority of people in the studies were taking two anti-epileptic drugs at enrolment. All the studies lasted 16–18 weeks. Each study included a phase of protocol-driven titration, the length of which depended on the dose to which a patient was randomised and lasted 4–8 weeks, followed by a maintenance phase when doses remained fixed and which lasted 8–12 weeks.

3.2 For each of the trials, the outcomes were evaluated in two ways. One way reflected the whole period of the trial, that is, the period combining both the titration and maintenance phases, and the second the maintenance phase alone. The manufacturer's submission focused on three main outcomes: the percentage of patients responding (response was defined as at least a 50% reduction in 28-day total partial onset seizure frequency from baseline to the end of the maintenance phase), percentage change from baseline in 28-day total partial onset seizure frequency, and the percentage of patients who were seizure-free. Only the results for the maintenance-phase analysis are reported below.

3.3 In the RESTORE 2 trial, a statistically significantly greater proportion of patients achieved a 50% or more reduction in the frequency of seizures with retigabine 600 mg and 900 mg compared with placebo (38.6% versus 18.9%, p < 0.001 and 47.0% versus 18.9%, p < 0.001 respectively). In the RESTORE 1 trial and study 205, statistically significantly greater proportions of patients achieved a 50% or more reduction in seizure frequency with retigabine.
1200 mg compared with placebo (55.5% versus 22.6%, \( p < 0.001 \) and 41.2% versus 25.6%, \( p < 0.01 \) respectively). In study 205, the results from the retigabine 600-mg and 900-mg doses were not statistically significantly different from placebo (27.7% versus 25.6%, \( p = 0.845 \) and 40.5% versus 25.6%, \( p = 0.057 \) respectively).

3.4 With regard to achieving freedom from seizures, one of the three trials (RESTORE 1) showed that more people receiving retigabine 1200 mg became free from seizures (7.6%) than people receiving placebo (1.5%, \( p = 0.027 \)). In study 205, the proportions of patients achieving freedom from seizures were 2.0% of those receiving retigabine 600 mg, 5.0% of those receiving retigabine 900 mg and 9.0% of those receiving retigabine 1200 mg compared with 4.0% receiving placebo (for comparisons of retigabine with placebo, \( p = 0.674 \), \( p = 0.714 \) and \( p = 0.304 \) respectively). In the RESTORE 2 trial, 3.2% of patients receiving retigabine 600 mg versus 1.2% receiving placebo (not reported), and 4.7% of those receiving retigabine 900 mg versus 1.2% receiving placebo, achieved freedom from seizures (\( p = 0.091 \)).

3.5 The following results describe the median change from baseline in the 28-day total partial onset seizure frequency. In the RESTORE 2 trial, patients receiving retigabine 600 mg experienced a median reduction in seizure frequency of 35.3% compared with a reduction of 17.4% in patients receiving placebo (\( p = 0.002 \)). Patients receiving retigabine 900 mg experienced a median reduction in seizure frequency of 44.3% compared with 17.4% with placebo (\( p < 0.001 \)). In the RESTORE 1 and study 205 trials, patients receiving retigabine 1200 mg experienced a median reduction in frequency of seizures compared with placebo of 54.5% versus 18.9% (\( p < 0.001 \)) and 43.7% versus 22.9% (\( p = 0.008 \)) respectively. In study 205, there were no statistically significant differences in seizure frequency between retigabine 600 mg or 900 mg and placebo (30.4% versus 22.9% [\( p = 0.536 \)]; 35.8% versus 22.9% [\( p = 0.170 \)] respectively).

3.6 The manufacturer presented data on adverse events for all patients included in the three trials who received at least one dose of retigabine (\( n = 813 \)). The overall frequency of any adverse event was 73.7%, 81.7% and 87.6% in the retigabine 600, 900 and 1200 mg/day groups respectively, and 74.5% in the
placebo group (n = 427). Rates of serious adverse events were 5.9% in the placebo group and 8.2%, 6.6% and 11.2% in the retigabine groups respectively. The manufacturer reported that the most common adverse events observed during treatment with retigabine that were also observed to have a dose–response relationship were dizziness (23%), somnolence (22%), confusional state (9%), tremor (8%), abnormal coordination (7%), memory impairment (6%), speech disorder (5%), blurred vision (5%), gait disturbance (4%), aphasia (4%), balance disorder (4%) and constipation (3%).

3.7 Treatment was discontinued because of adverse events in 11% of patients in the placebo group, 17% in the retigabine 600 mg/day group, 25% in the retigabine 900 mg/day group and 31% in the retigabine 1200 mg/day group. Dizziness was the most common reason for discontinuing retigabine. There were two deaths (including one sudden unexplained death from epilepsy [SUDEP]) among the 813 patients treated with retigabine and three deaths (including one SUDEP) among the 427 patients receiving placebo.

3.8 Health-related quality of life was evaluated in the RESTORE 1 and RESTORE 2 trials and presented for the maintenance phase. The trials used the Quality of Life in Epilepsy (QOLIE)-31 or QOLIE-31-P score and the Clinical Global Impression score. The manufacturer stated that in the RESTORE 1 trial, the mean scores for the QOLIE-31-P overall assessment were generally comparable between the retigabine and placebo groups at weeks 6 and 10. By week 18, the overall mean score for the QOLIE-31-P in the placebo group was slightly higher than in the retigabine group. In the RESTORE 2 trial there was a small general improvement within treatment groups in mean scores from baseline (randomisation) to weeks 4, 8, 16 and 20 in the overall assessment score. For the overall assessment, the mean scores did not show any significant difference between retigabine and placebo in quality of life by the end of the study.

3.9 Because all included trials were placebo controlled (that is, there were no trials comparing retigabine with an active comparator), the manufacturer compared retigabine with the identified comparators indirectly, using a network meta-analysis. The analyses used the following outcomes: proportion of patients with a reduction in 28-day total partial onset seizure frequency greater than or
equal to 50%, proportion of patients seizure free, and withdrawal because of adverse events. The manufacturer identified three trials of eslicarbazepine, three of lacosamide, five of pregabalin, three of tiagabine and three of zonisamide in the network meta-analysis. The manufacturer obtained the estimates for the efficacy of retigabine from study 205, RESTORE 1 and RESTORE 2. The manufacturer calculated pooled-effect estimates as both odds ratios and relative risks using both fixed-effects and random-effects models. The manufacturer presented results from the fixed-effects analysis in the submission, noting that the limited number of studies available by treatment meant that between-study statistical heterogeneity could not be comprehensively assessed. Not all trials provided data for all of the outcomes.

3.10 Not all comparators had data available for both the maintenance and double-blind period. Therefore two separate analyses were presented, one comparing retigabine with those treatments for which maintenance-phase data were available (that is, all treatments except for pregabalin) and another comparing retigabine with treatments for which double-blind phase data were available (that is, all treatments except for lacosamide and zonisamide). The maintenance-phase analysis for retigabine in the network meta-analysis was different from that in the clinical-effectiveness section of the manufacturer’s submission. This analysis included patients whose epilepsy responded to treatment in the fixed maintenance period and those whose epilepsy responded to treatment in the titration period but who withdrew because of adverse events.

3.11 The fixed-effect network meta-analysis showed that there were no statistically significant differences between retigabine and the comparator anti-epileptic drugs for all but one of the outcomes. For the outcome of patients who had achieved a 50% or more reduction in seizure frequency, the relative risk (RR) for the maintenance-phase analysis for retigabine versus eslicarbazepine was 1.25 (95% confidence interval [CI] 0.83 to 1.76), retigabine versus lacosamide RR 1.24 (95% CI 0.90 to 1.66), tiagabine versus retigabine RR 1.07 (95% CI 0.35 to 2.42) and zonisamide versus retigabine RR 1.07 (95% CI 0.70 to 1.53). For the same outcome during the double-blind period, the RR for retigabine versus eslicarbazepine was 1.01 (95% CI 0.60 to 1.54) and for tiagabine versus retigabine 1.46 (95% CI 0.80 to 2.47). A statistically significantly greater
proportion of patients achieved a 50% or more reduction in seizure frequency with retigabine compared with pregabalin (RR 0.67, 95% CI 0.44 to 0.97).

3.12 The manufacturer submitted a de novo economic model. This was a decision tree comparing retigabine with eslicarbazepine acetate, lacosamide, pregabalin, tiagabine, zonisamide and no treatment. The model discounted both costs and health effects at a rate of 3.5%. The time horizon of the model was 2 years. The model had four health states: seizure-free, response, no response and withdrawal from the adjunctive anti-epileptic drug because of adverse events. Seizure-free was defined as the percentage of patients free of seizures during a given therapy, response was defined as the proportion of patients who had achieved a 50% or more reduction in seizure frequency, and no response was defined as the proportion of patients whose frequency of seizures was reduced by less than half. The manufacturer obtained the estimates of efficacy from its network meta-analysis. It undertook two analyses: one for the maintenance period and the other for the whole double-blind period. The manufacturer assumed that patients who were seizure-free or responded to treatment would retain this benefit over the remaining 2-year time horizon of the model.

3.13 The manufacturer obtained the utilities for all health states from a published study (Selai et al. 2005) rather than from the quality-of-life measure collected in the retigabine trials. The manufacturer stated that it was not possible to map the output of the QOLIE-31-P from the retigabine trials to the EQ-5D preferred by NICE. The Selai study was designed to assess health-related quality of life by seizure frequency in patients with partial-onset epilepsy who were starting adjunctive therapy. The utility values used in the manufacturer's analyses were 0.9418 for seizure freedom, 0.90042 for a response to treatment, 0.8288 for non-response to treatment, and 0.8377 for withdrawal from treatment because of adverse events.

3.14 The manufacturer included the cost of treating seizures and the costs for acquiring, initiating, switching and monitoring drugs in the model. The cost of treating adverse events was included in a sensitivity analysis. Of those receiving retigabine, 33% incurred an additional cost of £23.76 per patient, reflecting the cost of recording an ECG. This cost was not incurred for patients
receiving a comparator drug. The model assumed that people whose disease did not respond or who discontinued treatment because of an adverse event switched to maintenance treatment (efficacy of placebo arm of anti-epileptic drug trials, at a cost equivalent to treatment with carbamazepine).

3.15 For the maintenance-phase analysis, the manufacturer's results showed that compared with no treatment, the incremental cost-effectiveness ratio (ICER) for retigabine was £66,334 per quality-adjusted life year (QALY) gained with an incremental cost of £1360 and incremental QALY of 0.021. Compared with eslicarbazepine and lacosamide, retigabine was associated with lower costs and more QALYs (0.0075 and 0.007 incremental QALYs and −£725 and −£91 incremental costs respectively). Compared with tiagabine, retigabine was associated with higher costs and fewer QALYs (−0.003 incremental QALYs and £283 incremental costs), and compared with zonisamide, retigabine was associated with lower costs but also fewer QALYs (−0.0033 incremental QALYs and −£893 incremental costs).

3.16 For the double-blind phase analysis, the manufacturer's results showed that compared with no treatment the ICER for retigabine was £62,608 per QALY gained with an incremental cost of £1194 and an incremental QALY of 0.019. Compared with pregabalin and tiagabine, retigabine was associated with higher costs and fewer QALYs (−0.012 and −0.013 incremental QALYs and £428 and £127 incremental costs respectively). Compared with eslicarbazepine, retigabine was associated with greater QALYs and lower costs (0.001 incremental QALYs and −£827 incremental costs).

3.17 The manufacturer completed a series of one-way sensitivity analyses including time horizon, time to withdrawal because of adverse events, utility values, cost of anti-epileptic drugs for those people stopping treatment because of non-response, discontinuation rate, discount rates, non-drug costs, costs of monitoring, costs of adverse events, baseline risk of events and the efficacy and costs of the anti-epileptic drugs. The manufacturer stated that none of the sensitivity analyses changed the overall findings of the base-case results.

3.18 Following the request for clarification from NICE, the manufacturer provided a scenario analysis that incorporated a 15-year time horizon, the costs and
utilities of adverse events, a treatment-switching cost for those people discontinuing treatment that had been applied in the economic analysis used in the draft update of 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' (NICE clinical guideline 20) and a rate reflecting the frequency of discontinuation of anti-epileptic drugs, which had also been used in the economic analysis in the draft update of NICE clinical guideline 20. The ICERs compared with no treatment decreased by approximately £20,000 per QALY gained, compared with the ICERs referred to in sections 3.15 and 3.16. However, the pattern of results for retigabine compared with the other comparators was unchanged; that is, retigabine was associated with higher costs and fewer QALYs than pregabalin and tiagabine, lower costs and the same or greater QALYs than lacosamide and eslicarbazepine, and lower costs and fewer QALYs than zonisamide.

3.19 The ERG noted that the decision problem in the manufacturer's submission focused on a subgroup of the population covered in the marketing authorisation, namely people requiring 'second-line' adjunctive therapies. The ERG stated that for this group the comparators eslicarbazepine, lacosamide, pregabalin, tiagabine and zonisamide were appropriate.

3.20 The ERG reported that the studies included in the manufacturer's submission were appropriate and that no relevant trials had been missed. The ERG compared the results for the double-blind and maintenance-phase analyses and noted that the results were generally different, but that the maintenance-phase analyses were not consistently better or worse than the double-blind phase analyses. The ERG noted that the maintenance-phase network meta-analysis differed from the clinical trial maintenance-phase analysis presented and included patients who responded in the fixed maintenance period and those who responded and then withdrew because of adverse events in the titration period.

3.21 The ERG, noting the manufacturer's two network meta-analyses (one for the maintenance phase and the other for the double-blind phase), considered that developing a single network of evidence would have enabled a single clinical- and cost-effectiveness analysis and would have been more appropriate.
3.22 The ERG stated that the use of a decision-tree de novo economic model was appropriate, but that use of a Markov model would have been more appropriate because it would have allowed more flexible movement between response categories, modelling of response to subsequent treatments, evaluation of the impact of withdrawing from anti-epileptic drugs over time and consideration of the uncertainty around those withdrawals.

3.23 The ERG stated that the economic model did not consider the sequencing of treatments. The ERG suggested that the model could have included all comparator treatments in different sequences. The ERG did not accept the validity of the modelled assumption that people whose epilepsy responds to treatment with retigabine do not experience any change in clinical response over time. The ERG judged that the manufacturer should have included discontinuation rates for anti-epileptic drugs in the base case.

3.24 The ERG judged that the 2-year time horizon of the model was inappropriate and would not capture all relevant costs and consequences because epilepsy is a chronic disease and requires treatment for years. The ERG also questioned whether it was reasonable for the manufacturer to assume that patients who withdrew from treatment with an adjunctive anti-epileptic drug would receive carbamazepine in its place and would incur the additional cost of carbamazepine but no additional clinical benefit.

3.25 The ERG undertook an exploratory analysis using the manufacturer's base-case economic model. In this analysis, the ERG incorporated data on pregabalin from the double-blind analysis into the maintenance-phase analysis of the other treatments. The ERG thereby constructed a single network of evidence that included retigabine plus all comparator treatments included in the manufacturer's submission compared with no treatment. The ERG presented the cost-effectiveness results in an incremental analysis that included all treatments, corrected the error in calculating resource use over the 15-year time horizon, and removed costs of carbamazepine for people withdrawing from adjunctive therapy and drug switching costs for those people not receiving adjunctive therapy. The most cost-effective treatment was then removed from the analysis and the remaining treatments analysed to identify the next best treatment. The analyses showed that pregabalin had the lowest
ICER at £24,527 per QALY gained compared with no treatment. The next best treatment was tiagabine with an ICER of £40,821 per QALY gained compared with no treatment. When both pregabalin and tiagabine were removed from the analysis, retigabine was the next best treatment with an ICER of £59,382 per QALY gained compared with no treatment. Retigabine dominated eslicarbazepine and lacosamide. Zonisamide had an ICER of £241,556 per QALY gained compared with retigabine.

3.26 The ERG also undertook an additional exploratory analysis using the economic model developed for the draft update of NICE clinical guideline 20. This analysis showed that pregabalin was the optimum treatment with an ICER of £13,962 per QALY gained compared with no treatment. When pregabalin had been tried and failed, the next best treatment was tiagabine, and after the failure of pregabalin and tiagabine, retigabine. The ICERs in these scenarios compared with no treatment were £33,673 and £42,604 per QALY gained for tiagabine and retigabine respectively. The analyses confirmed the pattern of results in the manufacturer's analyses and ERG exploratory analyses.

3.27 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TA232
4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of retigabine, having considered evidence on the nature of epilepsy and the value placed on the benefits of retigabine by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee discussed the clinical management of partial onset seizures. It heard from clinical specialists and patient experts that several anti-epileptic drugs are currently available for the treatment of partial onset seizures and that approximately 60% of people would require monotherapy only, and the remainder adjunctive therapy with a combination of anti-epileptic drugs. The Committee understood from the clinical specialists that as people receive larger numbers of anti-epileptic drugs, the likelihood of response decreases. The Committee heard from the clinical specialists that a decreasing response to a drug probably represented a worsening of disease rather than loss of effect of the drug. The Committee heard that some people with epilepsy do not achieve an adequate clinical response with currently available treatments. The clinical specialists and patient experts explained that people with epilepsy have different responses to particular treatments, and therefore would benefit from a range of available treatment options. The clinical specialists also explained that retigabine has a novel mode of action and therefore could be an important additional treatment option were it to provide response in those people whose epilepsy is considered resistant to current therapies.

4.3 The Committee sought the opinion of the clinical specialists and patient experts on the impact of partial onset seizures on people’s lives and on the experience of taking anti-epileptic drugs. The Committee heard that partial onset seizures are debilitating and affect both the individual and their immediate family. They can also have a wider impact through decreased opportunities to drive and take part in social and daily activities. Patient experts explained that public understanding of partial onset seizures can be limited, and a stigma can be attached to the condition that reduces quality of life for
people affected. The Committee also heard from the clinical specialists and patient experts that people with epilepsy particularly valued freedom from seizures as an outcome of treatment. However, reducing the frequency of seizures could be an important outcome for some patients, for example, for those who have seizures frequently, or when a change in treatment leads to less frequent seizures that are also milder and result in fewer adverse reactions.

4.4 The Committee discussed the decision problem in the manufacturer's submission and noted that the manufacturer had presented evidence for retigabine for a subgroup of the population covered by the marketing authorisation; that is, a population receiving retigabine after the failure of other adjunctive therapies. The Committee discussed the likely place of retigabine in clinical practice, the recommendations in existing NICE guidance, and the draft update of NICE clinical guideline 20. The Committee heard from clinical specialists that they would offer retigabine, at least initially, and consistent with the manufacturer's suggestion, to patients who had tried, but had not benefited from, carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate. However, the clinical specialists noted that in future, having gained experience with retigabine, clinicians may offer it to patients earlier in the treatment pathway. The Committee concluded that the comparator treatments included in the manufacturer's submission (that is, eslicarbazepine, lacosamide, pregabalin, tiagabine, vigabatrin and zonisamide) were in accordance with the way in which retigabine would be used in clinical practice. It noted comments from clinical specialists that pregabalin and tiagabine were not frequently used in routine practice in the NHS.

4.5 The Committee also discussed the requirements for monitoring the risk of QT prolongation and cardiac events when starting treatment with retigabine. The manufacturer confirmed that the summary of product characteristics recommended that an ECG should be recorded before starting treatment with retigabine for certain people, and recorded again when the maintenance dose is reached. The Committee noted that the manufacturer estimated that approximately 30% of people would require an ECG. However, it heard from the clinical specialists that until clinicians became familiar with retigabine, it
was likely that initially all patients would have an ECG, as had happened for
some other anti-epileptic drugs.

4.6 The Committee noted that for the RESTORE and 205 placebo-controlled trials,
two analyses were completed: one of the total double-blind period, which
included the forced-titration and maintenance phases, and one of just the
maintenance phase. The Committee heard from clinical specialists that, in
clinical practice, the increase in dosage (titration) from starting to final dose is
tailored to individual patients in order to ensure they tolerate a given treatment.
By contrast, the clinical trials mandated forced (protocol-driven) titration. The
Committee heard from the clinical specialists that the slower rate of titration in
clinical practice compared with the forced-titration period used in the clinical
trials meant that the results of the double-blind phase did not necessarily
represent the outcomes that would be observed in clinical practice. The
Committee discussed both analyses and noted that the results for the two
analyses were not consistently different from each other. The Committee
concluded that the trials had adequately shown that retigabine had
demonstrated efficacy compared with placebo.

4.7 The Committee discussed the quality-of-life results of the RESTORE trials. The
Committee noted that the results did not show a statistically significant
difference in quality of life between retigabine and placebo. However, the
Committee heard from patient experts that quality of life may not have been
improved because of the short time span of the trials. The patient experts
confirmed that it would be necessary for someone to see an improvement in
partial onset seizure frequency over a longer period of time to affect his or her
quality of life (for example, by reducing the fear of seizures and providing the
opportunity to obtain or regain a driving licence). The Committee accepted that
there may be limitations to the clinical trial data. However, it considered that
the benefits of retigabine on quality of life remained uncertain.

4.8 The Committee discussed the network meta-analysis completed by the
manufacturer to compare retigabine with the treatments included in the
manufacturer’s decision problem. The Committee noted that separate networks
had been completed: one where the data were available for the whole double-
blind period and one for data available for the maintenance phase. The
Committee heard from the ERG that the maintenance period analysis was not the same as that presented for the RESTORE trials and study 205; rather, it included patients who were responders in the maintenance-phase data as well as patients who responded and then withdrew because of adverse events in the titration phase. The Committee discussed the outcomes of the network meta-analysis and noted that the effects did not differ, apart from the response rate comparison between pregabalin and retigabine, which suggested that pregabalin was more efficacious than retigabine. The Committee heard from clinical specialists that although pregabalin reduced the frequency of seizures, they considered that it was unlikely to provide seizure freedom and therefore had limited use in clinical practice. The Committee concluded that none of the therapies included in the manufacturer's submission had been shown to be more or less clinically efficacious than the others.

4.9 The Committee discussed the adverse events associated with treatment with retigabine identified in the two RESTORE trials and study 205. The forced titration mandated in the clinical trials meant that the numbers of adverse events observed in the trials may not reflect clinical practice. The Committee discussed concerns raised by the patient experts about the risk of urinary-related adverse events with retigabine. The manufacturer explained that these problems were usually mild or moderate and resolved when the dosage of retigabine was reduced or treatment was stopped. The Committee discussed the risk of serious adverse reactions such as aphasia with retigabine. The Committee heard from clinical specialists and patient experts that in clinical practice there is a balance between adverse reactions to anti-epileptic drugs and the adverse effects of epilepsy. The patient experts and clinical specialists advised the Committee that they considered the adverse reactions associated with retigabine to be similar to those associated with other anti-epileptic drugs. The Committee concluded that the evidence did not suggest that the adverse reactions due to treatment with retigabine would be more serious than those caused by other available anti-epileptic drugs.

Cost effectiveness

4.10 The Committee discussed the manufacturer's model and its critique by the ERG. The Committee noted that the ERG had identified several limitations in
the submitted economic model and specifically in respect to its structure, time horizon, comparators, assumptions about treatment discontinuation and exclusion of adverse events. The Committee was aware that the manufacturer had submitted a decision-tree model, and that the ERG considered that a Markov model would have been more appropriate because it could have incorporated treatment sequencing, enabled a better understanding of uncertainty, and included estimates of mortality. However, the Committee understood that the ERG had provided an exploratory analysis using the Markov model developed for the draft update of NICE clinical guideline 20 with similar patterns of results across the different treatments to those from the decision-tree model.

4.11 The Committee discussed the 2-year time horizon of the model and whether this was of sufficient length to capture the relevant costs and benefits associated with treatments for epilepsy. The Committee heard from the clinical specialists that people with epilepsy are likely to take anti-epileptic drugs over a lifetime, but that they would switch between drugs during this time. The Committee recognised that, at the request of the ERG, the manufacturer had performed a scenario analysis extending the time horizon to 15 years. However, because the simulated patients entering the model resembled those in the trials (with an average age of 37 years), the Committee recognised that even 15 years may not reflect the lifetime nature of the condition. The Committee therefore concluded that the time horizon used in the manufacturer's base-case analysis was inadequate. It noted that in the scenario analysis the use of a longer time horizon had improved the cost effectiveness of the treatments.

4.12 The Committee noted that the manufacturer's analysis did not consider the possibility that patients discontinue drugs after 26 weeks of treatment. The Committee discussed whether it was appropriate to assume that everybody who responded to treatment continued on that treatment. The Committee heard that patients can switch treatments even after responding to treatment, but also after a worsening of seizure frequency or adverse reactions. The Committee did not consider it appropriate to exclude the possibility of discontinuation in the long term and considered it appropriate that this had been incorporated into a scenario analysis. The Committee was also aware
that, in the manufacturer's base case, only 33% of modelled patients had an ECG, however the clinical specialists had stated that at least initially all patients receiving retigabine would have an ECG. However, the Committee noted that this had been explored in the manufacturer's cost-effectiveness analyses and was satisfied that the costs for ECGs did not affect overall findings.

4.13 The Committee discussed the modelling of adverse events. The Committee noted that the manufacturer included adverse events in the base-case analysis only in terms of their impact causing withdrawal from treatment, rather than their impact on resource use and health-related quality of life. The Committee heard that there were differences in the adverse-event profiles of the anti-epileptic drugs, and that these differences were important to patients. The Committee noted that the manufacturer had provided a scenario analysis that included data on adverse events. The Committee concluded that the revised analysis including adverse events was appropriate.

4.14 The Committee noted that the manufacturer took EQ-5D utility estimates from the literature rather than from the RESTORE trials, and applied these to the model for the health states. The Committee discussed the utility data included in the manufacturer's model. The Committee noted that the estimates of utility appeared to be higher than would be expected. For example, a person with epilepsy no longer experiencing seizures had a utility of 0.94, which was higher than for the general population of the same age. The Committee questioned why the manufacturer had given values for utility that were higher for patients with more than one seizure per month than for patients with less than one seizure per month. The Committee also discussed concerns that, whereas the modelled values of utility showed a higher utility for no seizures compared with seizures more than halved in frequency, which in turn had a higher utility value than seizures less than halved in frequency, the trials showed no difference in quality of life and yet showed that retigabine reduced the frequency of seizures. The Committee noted that the difference between the values in the model for no response (less than 50% reduction in seizure frequency) and response (50% or more reduction in seizure frequency) was twice that of the difference between response and seizure freedom. The Committee understood that, by contrast, patient experts valued seizure freedom more than a reduction
in the number of seizures. The Committee therefore agreed that the utility estimates were subject to a high degree of uncertainty. However, it accepted that no more appropriate utility values were available.

4.15 The Committee discussed whether it was appropriate for the manufacturer to have omitted mortality from the model. The Committee noted that people with epilepsy who are free of seizures have a lower death rate than people with epilepsy who are not free of seizures. The Committee was also aware that the manufacturer had excluded mortality, citing the young starting age of the average modelled patient (37 years) and the short time horizon (2 years). In addition, the manufacturer considered the differences in mortality to be small between not seizure-free and seizure-free patients. The Committee was also aware that in the clinical trials, patients receiving retigabine were more likely to be free of seizures than those receiving placebo. The Committee recognised that the decision-tree model used by the manufacturer did not allow mortality to be included. The Committee concluded that had it been possible for the manufacturer to extend the time horizon of the model and modelled mortality, this would have increased the health-related quality-of-life benefits associated with treatment and improved the cost effectiveness compared with no treatment. However, it noted that mortality had been included in the economic model used for the draft update of NICE clinical guideline 20 and that when the ERG had incorporated retigabine into this model a similar pattern of results between treatments was observed.

4.16 The Committee noted that one of the comparators in the model was 'no treatment', and that this included the cost of carbamazepine, but with no benefit from treatment. The Committee heard from the clinical specialists that if an anti-epileptic drug did not result in an adequate reduction in the frequency of partial onset seizures, in clinical practice an alternative anti-epileptic drug would be given. Alternatively, if there were no untired options, a patient would revert to the combination of anti-epileptic drugs that gave the best possible balance between seizure control and tolerability. The clinical specialists did not consider that including carbamazepine in the analysis as 'no treatment' was appropriate, because patients would have already tried and stopped carbamazepine at a much earlier point in the clinical pathway. The anti-epileptic drugs patients would try at this point in the treatment pathway would
likely be those identified in the manufacturer's decision problem and that therefore an active comparator, rather than no comparator, was appropriate. The Committee therefore agreed that although it should be mindful of the ICERs compared with 'no treatment', it considered it more appropriate to base its decisions on the cost effectiveness of retigabine in relation to eslicarbazepine, lacosamide, pregabalin, tiagabine and zonisamide.

4.17 The Committee considered costs of the treatments included in the manufacturer's decision problem. It noted that the cost of the anti-epileptic drugs ranged from approximately £2.30 to £6.40 a day and that, at approximately £3.80, retigabine had a cost comparable to the other anti-epileptic drugs. The Committee heard from clinical specialists that in practice they would most likely start patients on doses smaller than the licensed dose, in order to increase the chance that a patient tolerates the drug. Therefore, the Committee concluded that there was some uncertainty about the total costs of the drugs, but that retigabine appeared to have a cost comparable to the other anti-epileptic drugs used at the point in the clinical pathway reflected by the decision problem.

4.18 The Committee discussed the manufacturer's cost-effectiveness estimates and the exploratory analyses carried out by the ERG. The Committee agreed that the ICERs presented were all highly uncertain because of the limitations in the availability of data and in the manufacturer's analysis. In addition, the Committee noted that in all the analyses the differences in both costs and QALYs between retigabine and comparator treatments were very small, making the estimates of cost effectiveness extremely sensitive to small changes in the model. The Committee noted that compared with 'no treatment', which was not specified in the scope and considered not to be an appropriate comparator, the analyses for retigabine consistently suggested ICERs of £40,000–£60,000 per QALY gained. However, compared with the other treatments, retigabine was sometimes associated with fewer QALYs and more costs, and at other times associated with more QALYs and less costs. The Committee understood from the clinical specialists that the two treatments with less costs than retigabine (that is, pregabalin and tiagabine) were not used widely in clinical practice in the NHS. On balance, the Committee was persuaded that it was appropriate to consider retigabine compared with
eslicarbazepine, lacosamide, pregabalin, tiagabine and zonisamide rather than 'no treatment', and that on this basis retigabine had been shown to have comparable efficacy and cost, given the uncertainties present. Despite its reservations about the validity of the cost-effectiveness estimates obtained from the economic evaluation the Committee concluded that retigabine could be considered a cost-effective use of NHS resources when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate has not provided an adequate response or has not been tolerated.

Summary of Appraisal Committee's key conclusions

<table>
<thead>
<tr>
<th>TA232</th>
<th>Appraisal title: Retigabine for the adjunctive treatment of partial onset seizures in epilepsy</th>
<th>Section</th>
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<tr>
<td></td>
<td>Key conclusion</td>
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<td></td>
<td>Retigabine is recommended as an option for the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate has not provided an adequate response, or has not been tolerated. The Committee agreed that the ICERs presented were all highly uncertain because of the limitations in the availability of data and in the manufacturer's analysis. On balance, the Committee was persuaded that it was appropriate to compare retigabine with eslicarbazepine, lacosamide, pregabalin, tiagabine and zonisamide rather than 'no treatment'. Compared with these treatments, retigabine was sometimes associated with fewer QALYs and more costs, and at other times associated with more QALYs and fewer costs. The Committee understood from the clinical specialists that the two treatments with fewer costs than retigabine (that is, pregabalin and tiagabine) were not used widely in clinical practice in the NHS.</td>
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<td></td>
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<td>4.18</td>
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<td>Current practice</td>
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</table>
Clinical need of patients, including the availability of alternative treatments

The main aim of treatment is to reduce the impact of the condition on patients and their families. This includes reduced quality of life and decreased opportunities to drive and take part in social activities.

There are several anti-epileptic drugs currently available for the treatment of partial onset seizures. Approximately 60% of people require monotherapy only, and the remainder adjunctive therapy with a combination of anti-epileptic drugs.

People with epilepsy are likely to take anti-epileptic drugs over a lifetime, but that they would switch between drugs during this time.

<table>
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<th>The technology</th>
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<tr>
<td>Prop. benefits of the technology</td>
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<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
</tr>
<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
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<tr>
<td>Adverse effects</td>
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Evidence for clinical effectiveness

| Availability, nature and quality of evidence | The Committee discussed the results of the analyses of the two RESTORE trials and 205 study for the total double-blind period and the maintenance phase. The manufacturer presented a network meta-analysis to compare retigabine with the treatments included in the manufacturer's decision problem. | 4.6 4.8 |
| Relevance to general clinical practice in the NHS | The Committee heard from the clinical specialists that the slower rate of titration in clinical practice compared with the forced-titration period used in the clinical trials meant that the results of the double-blind phase did not necessarily represent the outcomes that would be observed in clinical practice. | 4.6 |
| Uncertainties generated by the evidence | The Committee noted that the results did not show a statistically significant difference in quality of life between retigabine and placebo. However, the Committee heard from patient experts that quality of life may not have been improved because of the short time span of the trials. The Committee accepted that there may be limitations to the clinical trial data. However, it considered that the benefits of retigabine on quality of life remained uncertain. | 4.7 |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | N/A |
The Committee concluded that the trials had adequately shown that retigabine had demonstrated efficacy compared with placebo. The Committee concluded that none of the therapies included in the manufacturer's submission had been shown to be more or less clinically efficacious than the others.

### Evidence for cost effectiveness

| Availability and nature of evidence | The manufacturer submitted a de novo economic model. This was a decision tree comparing retigabine with eslicarbazepine acetate, lacosamide, pregabalin, tiagabine, zonisamide and no treatment. The Committee agreed that the comparator treatments included in the manufacturer's submission (that is, eslicarbazepine, lacosamide, pregabalin, tiagabine, vigabatrin and zonisamide) were appropriate, and that it should consider the ICERs for retigabine in relation to these treatments rather than against no treatment. | 4.10 4.18 |
The Committee noted that the ERG had identified several limitations in the submitted economic model and specifically in respect to its structure, time horizon, comparators, assumptions about treatment discontinuation and exclusion of adverse events. The Committee concluded that the time horizon used in the manufacturer's base-case analysis was inadequate and that a longer time horizon improves the cost effectiveness.

The Committee noted that the manufacturer's analysis did not consider the possibility that patients discontinue drugs after 26 weeks of treatment. The Committee did not consider it appropriate to exclude the possibility of discontinuation in the long term and considered it appropriate that this had been incorporated into a scenario analysis.

The Committee noted that mortality had not been included in the model. The Committee concluded that had it been possible for the manufacturer to extend the time horizon of the model and modelled mortality, this would have increased the health-related quality-of-life benefits associated with treatment and improved the cost effectiveness compared with no treatment.

The Committee considered costs of the treatments included in the manufacturer's decision problem. The Committee concluded that there was some uncertainty about the total costs of the drugs, but that retigabine appeared to have a cost comparable to the other anti-epileptic drugs used at the point in the clinical pathway reflected by the decision problem.
<table>
<thead>
<tr>
<th>Incorporation of health-related quality-of-life benefits and utility values</th>
<th>The Committee agreed that the utility estimates were subject to a high degree of uncertainty. However, it accepted that currently no more appropriate utility values were available. No potential health-related benefits were identified that were not included in the economic model.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</td>
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<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>N/A</td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>In all analyses, the difference in both costs and QALYs between retigabine and comparator treatments was very small, making the estimates of cost effectiveness extremely sensitive to small changes in the model.</td>
</tr>
</tbody>
</table>
Most likely cost-effectiveness estimate (given as an ICER) | The Committee noted that against the other treatments, retigabine was sometimes associated with fewer QALYs and more costs, and at other times associated with more QALYs and lower costs. The Committee understood from the clinical specialists that the two treatments with lower costs than retigabine (that is, pregabalin and tiagabine) were not used widely in clinical practice in the NHS.

<table>
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<tr>
<th>Additional factors taken into account</th>
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<tr>
<td>Patient access schemes (PPRS)</td>
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<tr>
<td>End-of-life considerations</td>
</tr>
<tr>
<td>Equalities considerations and social value judgements</td>
</tr>
</tbody>
</table>
5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient with epilepsy has partial onset seizures and the doctor responsible for their care thinks that retigabine is the right treatment, it should be available for use, in line with NICE’s recommendations.

5.3 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TA232).

- A costing statement explaining the resource impact of this guidance.
6 Recommendation for further research

6.1 The Committee considered that research investigating the health-related quality of life of people with epilepsy would be of value.
7 Related NICE guidance

Published


Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (partial update of NICE clinical guideline 20).
8 Review of guidance

8.1 The guidance on this technology will be considered for review in June 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon

Chief Executive

July 2011
Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair) Consultant Physician, Addenbrooke's Hospital

Dr Ray Armstrong Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Peter Barry Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor John Cairns Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

Professor Fergus Gleeson Consultant Radiologist, Churchill Hospital, Oxford
Mrs Eleanor Grey Lay member

Mr Sanjay Gupta Younger Person's Disability Service Case Manager, Southwark Health and Social Care, Southwark Primary Care Trust

Dr Neil Iosson General Practitioner

Mr Terence Lewis Lay member

Dr Ruairidh Milne Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Rubin Minhas General Practitioner and Clinical Director, British Medical Journal Evidence Centre

Dr Peter Norrie Principal Lecturer in Nursing, DeMontfort University

Dr Sanjeev Patel Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford Consultant Physician, Frenchay Hospital, Bristol

Dr Casey Quinn Lecturer in Health Economics, Division of Primary Care, University of Nottingham

Dr John Rodriguez Assistant Director of Public Health, NHS Eastern and Coastal Kent

Mr Alun Roebuck Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Mr Navin Sewak Primary Care Pharmacist, NHS Hammersmith and Fulham

Mr Cliff Snelling Lay member

Professor Ken Stein (Vice Chair) Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter
Professor Andrew Stevens  Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

B Guideline representatives

The following individual, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, was invited to attend the meeting to observe and to contribute as an adviser to the Committee.

- Susan Latchem, Operations Director, National Clinical Guidelines Centre

C NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker  Technical Lead

Zoe Garrett  Technical Adviser

Jeremy Powell  Project Manager
Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the NHS Centre for Reviews and Dissemination, and Centre for Health Economics, University of York:


B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on [technology] by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- GlaxoSmithKline

II Professional/specialist and patient/carer groups:

- Association of British Neurologists
- Epilepsy Action
- International League Against Epilepsy UK
- National Society for Epilepsy
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:
Retigabine for the adjunctive treatment of partial onset seizures in epilepsy

- Department of Health
- NHS Southampton City
- NHS Southwark
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Eisai
- Medicines and Healthcare products Regulatory Agency
- Healthcare Improvement Scotland
- Novartis
- Pfizer
- Sanofi-Aventis

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on retigabine by providing oral evidence to the Committee.

- Professor Ley Sander, National Society for Epilepsy Professor of Neurology and Clinical Epilepsy & Consultant Neurologist, University College London Institute of Neurology & the National Hospital for Neurology and Neurosurgery, nominated by GlaxoSmithKline – clinical expert
- Professor Phil Smith, Consultant Neurologist, Cardiff and Vale University Health Board, nominated by the Welsh Assembly Government – clinical expert
- Kathy Bairstow, nominated by Epilepsy Action – patient expert
• Sari Huttunen, nominated by Epilepsy Action – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

• GlaxoSmithKline
Changes after publication

**March 2014:** implementation section updated to clarify that retigabine is recommended as an option for treating partial onset seizures in epilepsy. Additional minor maintenance update also carried out.
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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