

## Medicine Reimbursement

■ **eAppendix Table.** Comparison of Clinical and Pharmacoeconomic Analysis When Agencies' Recommendations Are Discordant

Drug	CDR Recommendation	Reasons for CDR Decision	PBAC Recommendation	Reasons for PBAC Decision
Erlotinib	List with criteria	<p><b>Clinical:</b> increased mean survival compared with placebo from 4.7 to 6.7 months and percent surviving at 1 year from 21.5% to 31.2%; survival benefit achieved without significant decrease in quality of life</p> <p><b>Pharmacoeconomic:</b> cost-effective compared with docetaxel and has incremental cost-effectiveness of CAN \$71,000 per life-year gained compared with best supportive care</p>	Do not list	<p><b>Clinical:</b> RCT comparing erlotinib with best supportive care demonstrated statistically significant benefits of erlotinib regarding all event rates; indirect comparison with docetaxel showed no statistically significant difference in survival</p> <p><b>Pharmacoeconomic:</b> cost-effectiveness compared with docetaxel not demonstrated and uncertain cost-effectiveness in comparison with best supportive care</p>
Insulin detemir	Do not list	<p><b>Clinical:</b> in type 1 diabetes, 4 of 5 RCTs showed no statistically significant differences in control of A1C compared with NPH insulin; 1 RCT favored insulin detemir; 0 of 5 RCTs reported statistically significant differences compared with NPH insulin in incidence of major hypoglycemic or major nocturnal hypoglycemic episodes; in type 2 diabetes, 2 of 5 RCTs found insulin detemir inferior to NPH insulin in control of A1C; 0 of 5 RCTs reported statistically significant differences compared with NPH insulin in incidence of major hypoglycemic or major nocturnal hypoglycemic episodes</p> <p><b>Pharmacoeconomic:</b> cost per 100 units is 3 times greater than NPH insulin; economic model was in type 1 diabetes only, and assumptions of improved control of A1C and reduced hypoglycemia compared with NPH insulin not supported</p>	Restricted benefit	<p><b>Clinical:</b> insulin detemir no worse in controlling A1C than NPH insulin for both type 1 and 2 patients combined and type 1 patients alone; no significant differences in major hypoglycemic events compared with NPH insulin in type 1 and 2 diabetes</p> <p><b>Pharmacoeconomic:</b> doubts about economic model and resulting high and uncertain cost-effectiveness ratios compared with NPH insulin and price advantage requested over NPH insulin not justified; PBAC willing to accept listing for type 1 diabetes if manufacturer indicated an acceptable basis for cost-effectiveness recommendation</p>
Insulin glargine	Do not list	<p><b>Clinical:</b> RCTs did not find statistically or clinically significant differences between insulin glargine and NPH (or ultralente) insulin in serious morbidity or glycemic control in patients with either type 1 or 2 diabetes; no significant differences between insulin glargine and NPH (or ultralente) insulin in incidence of severe symptomatic hypoglycemia in either type 1 or 2 diabetes; variable results for incidence of overall and nocturnal hypoglycemia for both type 1 and 2 diabetes; quality-of-life results inconsistent for type 1 diabetes trials and no differences between groups in type 2 diabetes trials</p> <p><b>Pharmacoeconomic:</b> assumptions in model of lower level of A1C without increasing incidence of hypoglycemia compared with NPH insulin not supported; cost is about 3.5 times that of NPH insulin</p>	Unrestricted listing	<p><b>Clinical:</b> event rate reduction for severe events not significant compared with NPH insulin; lack of evidence of long-term benefit</p> <p><b>Pharmacoeconomic:</b> price advantage compared with NPH insulin not justified due to uncertainties with economic model and resulting cost-effectiveness ratios; PBAC willing to accept listing for type 1 diabetes if manufacturer indicated an acceptable basis for cost-effectiveness recommendation</p>

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■ **eAppendix Table.** Comparison of Clinical and Pharmacoeconomic Analysis When Agencies' Recommendations Are Discordant (Continued)

Drug	CDR Recommendation	Reasons for CDR Decision	PBAC Recommendation	Reasons for PBAC Decision
Pregabalin	Do not list	<p><b>Clinical:</b> no trials comparing pregabalin with other therapies and all trials of relatively short duration; compared with placebo, statistically significant improvements in numerical pain rating scales and patient global impression of change in pain; high withdrawal rates decrease confidence in study results</p> <p><b>Pharmacoeconomic:</b> costs are higher than tricyclic antidepressants; interpretation of pharmacoeconomic model submitted by manufacturer that compared pregabalin with gabapentin limited by difficulty in determining dose equivalency</p>	Restricted benefit	<p><b>Clinical:</b> indirect estimates of comparative treatment effect are not statistically significant between pregabalin and gabapentin at the nominated doses for either effectiveness or toxicity</p> <p><b>Pharmacoeconomic:</b> PBAC estimated therapeutically equivalent doses of pregabalin and gabapentin (different from those suggested by manufacturer) and approved drug based on equivalent cost between pregabalin and gabapentin at these doses</p>

Drug	CDR Recommendation	Reasons for CDR Decision	SMC Recommendation	Reasons for SMC Decision
Atomoxetine	Do not list	<p><b>Clinical:</b> not superior to methylphenidate products; atomoxetine not contraindicated in patients with tics or Tourette's syndrome but methylphenidate can be used in these patients; adverse effects qualitatively similar to those from methylphenidate and dexamphetamine</p> <p><b>Pharmacoeconomic:</b> clinical experience with use of other less expensive agents for adult ADHD; cost is higher than that of methylphenidate products or dexamphetamine</p>	Accepted for restricted use	<p><b>Clinical:</b> prolonged-release methylphenidate had significantly larger response rate than atomoxetine in the stimulant-responder group, but no difference in stimulant-naïve group; time to protocol-defined relapse significantly longer with continued treatment with atomoxetine than with placebo; gastrointestinal effects (vomiting) significantly more common than with methylphenidate; both methylphenidate and atomoxetine well tolerated</p> <p><b>Pharmacoeconomic:</b> costs per QALY for the subgroups in whom stimulant medication is contraindicated are in the range of £12,000-£13,200; costs per QALY for the stimulant-failure population are in the range of £16,000-£18,400; atomoxetine has higher acquisition costs than methylphenidate with no overall greater benefit</p>

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Drug	CDR Recommendation	Reasons for CDR Decision	SMC Recommendation	Reasons for SMC Decision
Efalizumab	List with criteria	<p><b>Clinical:</b> associated with statistically significant and clinically important improvements in physician and patient global scores; possible potential for significant worsening of psoriasis after discontinuation in partial responders or nonresponders; long-term safety and effectiveness unclear</p> <p><b>Pharmacoeconomic:</b> 1 year of treatment cost CAN \$21,000; felt that manufacturer's cost-effectiveness study overestimated efficacy and underestimated costs relative to standard care</p>	Not recommended for use	<p><b>Clinical:</b> response significantly better than that seen with placebo on psoriasis area severity score; rate of SAEs and infections similar to rate with placebo in most trials; however, in single largest trial there were more SAEs with efalizumab than with placebo; no data from direct comparisons between efalizumab and other systemic treatments for psoriasis</p> <p><b>Pharmacoeconomic:</b> manufacturer attempted to convert trial outcomes into QALYs; however, the evidence base for carrying this out was very limited; economic quality-of-life estimate (utility) for patients who respond to treatment was based on an explicit assumption that was not justified in the submission and lacks face validity</p>
Fosamprenavir	List with criteria	<p><b>Clinical:</b> fosamprenavir-ritonavir had an effect on viral load and CD4+ count similar to that of nelfinavir; no evidence to support equivalence of fosamprenavir-ritonavir to lopinavir-ritonavir; adverse effect profile similar to that of other protease inhibitors</p> <p><b>Pharmacoeconomic:</b> comparable in price to other available protease inhibitors</p>	Accepted for use	<p><b>Clinical:</b> fosamprenavir-ritonavir showed efficacy comparable to that of nelfinavir in treatment-naïve patients but was not comparable to lopinavir-ritonavir in patients with previous protease inhibitor exposure; predictable and manageable safety profile</p> <p><b>Pharmacoeconomic:</b> for treatment-naïve patients, extra cost of the fosamprenavir-based regimen is justified by the lower pill burden and likely increased patient adherence to treatment schedules; for treatment-experienced patients, similar costs and outcomes compared with other treatment regimens; economics study design suffered from several weaknesses</p>
Mycophenolate sodium	List with criteria	<p><b>Clinical:</b> no difference in efficacy, safety, and tolerability between mycophenolate sodium enteric-coated tablets and mycophenolate mofetil solid formulations</p> <p><b>Pharmacoeconomic:</b> at recommended adult doses, mycophenolate sodium will cost CAN \$0.83 per day less than mycophenolate mofetil</p>	Accepted for use	<p><b>Clinical:</b> no difference in efficacy, safety, and tolerability between mycophenolate sodium enteric-coated tablets and mycophenolate mofetil solid formulations; anticipated improvement in gastrointestinal side effects not yet shown</p> <p><b>Pharmacoeconomic:</b> based on clinical data that mycophenolate sodium is equally efficacious and safe compared with mycophenolate mofetil, the cost per day is £9.07 for mycophenolate mofetil and £8.17 for mycophenolate sodium</p>

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Drug	CDR Recommendation	Reasons for CDR Decision	SMC Recommendation	Reasons for SMC Decision
Pegaptanib	Do not list	<p><b>Clinical:</b> compared with sham treatment, there were statistically significant improvements in the number of patients who experienced loss of less than 3 lines of visual acuity and the number of patients who gained <math>\geq 3</math> lines of visual acuity; unable to assess effectiveness beyond 1 year; benefits assessed in study eye only, and effects on overall visual function using both eyes not clear</p> <p><b>Pharmacoeconomic:</b> costs CAN \$7960 per year; economic model reported incremental cost-effectiveness of CAN \$59,000 per QALY compared with standard care, but analysis conducted over a lifetime time horizon, although clinical benefits beyond 1 year uncertain</p>	Accepted for restricted use	<p><b>Clinical:</b> rate of decline was significantly less in the pegaptanib group than in sham treatment group; significant advantages for pegaptanib over control in the proportion of patients experiencing severe vision loss, progression to legal blindness, and maintenance or gain in vision; rate of discontinuation because of adverse events during the first year was 1% in both the pegaptanib and the sham injection groups; studies only designed to assess medication in first year of treatment</p> <p><b>Pharmacoeconomic:</b> cost per QALY of £15,000 after 2 years of treatment; key strength of the clinical evidence is that the manufacturer has provided a targeted treatment option based on clinical opinion regarding what is likely to happen in practice in Scotland; manufacturer has justified the extrapolation beyond the 2-year trial data to a 10-year time horizon; resource use estimates were based on clinical opinion and Scottish data have been incorporated where appropriate</p>

A1C indicates glycosylated hemoglobin; ADHD, attention-deficit/hyperactivity disorder; CDR, Common Drug Review; PBAC, Pharmaceutical Benefits Advisory Committee; QALY, quality-adjusted life-year; RCT, randomized controlled trial; SAE, serious adverse event; SMC, Scottish Medicines Consortium.