Scottish Medicines Consortium

duloxetine 30mg and 60mg capsules (Cymbalta®) No. (285/06)

Eli Lilly and Company Limited/Boehringer Ingelheim

4 August 2006

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

ADVICE: following a full submission

duloxetine (Cymbalta®) is accepted for restricted use for the treatment of diabetic peripheral neuropathic pain in adults**.**

Duloxetine relieved peripheral neuropathic pain compared with placebo in patients with diabetes. It is restricted to initiation by prescribers experienced in the management of diabetic peripheral neuropathic pain as 2nd or 3rd line therapy.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Duloxetine 30mg and 60mg capsules (Cymbalta®)

Indication

Treatment of diabetic peripheral neuropathic pain in adults.

Dosing information

Starting and recommended maintenance dose is 60mg daily, with or without food. Some patients may benefit from a higher dose, up to a maximum of 120mg per day in evenly divided doses.

UK launch date

July 2005

Comparators

Tricyclic antidepressants, although unlicensed for this indication, are recommended by the Scottish Intercollegiate Guidelines Network (SIGN) as first-line therapy for painful diabetic neuropathy and by the National Institute for Health and Clinical Excellence (NICE) for this condition after failure of simple analgesics and local measures. Gabapentin is licensed for treatment of neuropathic pain and is also recommended by SIGN and NICE as a treatment option after tricyclic antidepressants. Pregabalin is licensed for the treatment of peripheral neuropathic pain in adults, however, the Scottish Medicines Consortium (SMC) has issued advice that it is not recommended for use within NHS Scotland for this indication. Capsaicin cream is licensed for symptomatic management of painful diabetic peripheral polyneuropathy and SIGN recommended that it should be considered for the relief of localised neuropathic pain.

Cost of relevant comparators

Drug	Usual daily dose	Annual cost
Duloxetine	**60-120mg**	**£360-£721**
Pregabalin	150-600mg	£837*
Gabapentin	900-1800mg	£541-£1158**
Nortriptyline****	25-75mg	£89-268
Carbamazepine	400-1600mg	£96-£407
Carbamazepine (Tegretol Retard®)	400-1600mg	£68-£269
Amitriptyline****	25-75mg	£16-£50
Capsaicin 0.075% cream (Axsain®)	Applied three to four times daily	£138***

** Any dose of pregabalin (150-600mg daily) prescribed in two divided doses costs £64.40/28 days and prescribed in three divided doses costs £96.60/28 days which would increase the annual cost to £1255 .*

*** prices based on gabapentin 300mg capsules (for the 900mg dose) and 600mg capsules (for the 1800mg dose)*

**** cost for capsaicin cream is based on the assumption that a 45g tube (costing £12.15) lasts 28 days Costs from eVADIS 28th July 2006*

***** This is unlicensed use for amitriptyline and noritriptyline*

Summary of evidence on comparative efficacy

Duloxetine is a combined serotonin and noradrenaline reuptake inhibitor. Its pain inhibitory action is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

Two phase 3 and one phase 2 double-blind placebo-controlled 12-week studies recruited in total over 1000 adults with pain, due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus, which had begun in the feet with relatively symmetrical onset and been present daily for at least 6 months. The diagnosis was confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument and patients also had a mean weekly score of at least 4 on the 24-hour average pain score, which was rated daily on an 11-point Likert scale where 0=no pain and 10=worst possible pain. Patients were randomly assigned equally to one of three groups: duloxetine 60mg once daily (OD), duloxetine 60mg twice daily (BD), or placebo. Patients in the 60mg BD groups were initiated at a lower dose for the first 3 days of treatment. In all the studies the primary endpoint was change from baseline to week 12 or last visit in weekly mean 24-hour average pain scores, which were recorded daily by the patient on the 11-point Likert scale. Differences between each treatment group and placebo were assessed via analysis of covariance (ANCOVA) in the intention to treat populations who had a baseline and at least one post-baseline efficacy assessment. These were the primary analyses in the phase 3 trials. Duloxetine 60mg OD and 60mg BD, compared with placebo, significantly reduced weekly mean 24-hour average pain score from baseline to last visit. The proportions of patients achieving reductions of at least 30% and 50% from baseline to last visit for this outcome were generally significantly greater in these treatment groups compared to placebo, except for the proportion of patients achieving at least a 50% reduction with duloxetine 60mg BD in one of the phase 3 trials. These results are summarised in the table below.

Weekly mean 24-hour average daily pain scores in phase 2 and 3 placebo-controlled 12-week trials of duloxetine in patients with diabetic peripheral neuropathic pain

Study	Treatment group (number of randomised patients)	Weekly mean 24-hour daily pain score			
		Mean		Number (%) of responders[X]	
		Baseline	Change[Y]	≥30%	≥50%
Phase 3 (Study A)	Placebo (n=106)	5.9	-1.39	44 (42%)	29 (27%)
	Duloxetine 60mg OD (n=110)	6.1	-2.72*	69 (63%)*	47 (43%)*
	Duloxetine 60mg BD (n=111)	6.2	-2.84*	77 (69%)*	59 (53%)*
Phase 3 (Study B)	Placebo (n=113)	5.5	-1.60	49 (43%)	34 (30%)
	Duloxetine 60mg OD (n=113)	5.5	-2.50*	77 (68%)*	56 (50%)*
	Duloxetine 60mg BD (n=114)	5.7	-2.47*	73 (64%)*	45 (39%)
Phase 2	Placebo (n=111)	5.8	-1.69	52 (47%)	29 (26%)
	Duloxetine 20mg OD (n=111)	5.9	-2.14	57 (51%)	46 (41%)*
	Duloxetine 60mg OD (n=112)	6.0	-2.86*	72 (64%)*	55 (49%)*
	Duloxetine 60mg BD (n=109)	5.9	-3.14*	71 (65%)*	57 (52%)*

** significant versus placebo; X = response defined as at least 30% or 50% reduction from baseline to last visit in weekly mean 24-hour average daily pain score; Y = least squares mean change from baseline from ANCOVA*

Quality of life

In the short form 36 (SF 36) survey generally, but not in all cases, the duloxetine treated groups produced significant improvements compared to placebo of between 4 and 8 points, on a 100 point scale, in bodily pain, general health and mental health subscales. In the first

phase 3 study SF 36 physical function and role physical scores significantly improved in duloxetine treated groups compared to placebo by between 8 and 13 points. The Euro Qol EQ-5D score, where full health=1.0, significantly improved in the duloxetine treated groups compared to placebo by 0.06 in 2 of the 3 studies.

Summary of evidence on comparative safety

No new safety concerns for duloxetine were identified in the trials described previously.

Summary of clinical effectiveness issues

The duloxetine summary of product characteristics states that no conclusive efficacy data for treatment longer than 12 weeks duration are available from placebo-controlled studies in diabetic peripheral neuropathic pain. As this is a chronic condition, further evaluation of the long-term efficacy of duloxetine would be required to estimate any effects on progression of neuropathic pain over the longer term that could be expected in practice.

The trials described previously excluded patients with co-morbid conditions and concomitant medications that might have interfered with interpretation of efficacy or safety data. Thus, it is possible that the trial population and size of benefits observed with duloxetine within it may differ from the Scottish population in which duloxetine might be used in practice.

Prior to enrolment 48-66% of patients had had at least one previous medication for diabetic peripheral neuropathic pain.

Controlled studies did not demonstrate any benefit in using the 120mg versus 60mg dosing schedule.

There are no trials directly comparing duloxetine with any alternative treatments for diabetic peripheral neuropathic pain. Therefore, efficacy and safety of duloxetine in practice relative to these treatments are unknown.

Summary of comparative health economic evidence

The manufacturer submitted a cost utility analysis, using a decision tree model. This suggested that duloxetine was cost saving and delivered slightly more quality adjusted life years (QALYs), when used as second line, than gabapentin.

Patients enter the model after failing on analgesics and all receive a tricyclic antidepressant (unlicensed) as first line. In the standard care arm second line is gabapentin followed by tramadol. The comparator is duloxetine, gabapentin, then tramadol. A patient switches lines because of a less than 30% improvement in baseline pain score or an intolerable adverse event.

The clinical effectiveness rates and adverse events for duloxetine came from the clinical trials previously discussed; equivalent data were provided from comparator trials.

The model included appropriate drug and management costs (GP and outpatient clinic) and used utility values which were derived from the quality of life values measured in the trials. For

a cohort of 1,000 patients, the results were a cost saving of around £68 per patient and an additional 0.002 QALYs over 6 months. Extensive sensitivity analyses showed the result was sensitive to the price of gabapentin and the relative clinical response rates.

Patient and public involvement

Patient Interest Group Submission: Diabetes UK Scotland

Budget impact

The manufacturer assumed that in 2006, 64 (0.4% of population) patients would be treated with duloxetine, rising to 1,240 (7.7%) in 2010. The associated annual cost of duloxetine would be £9,900 rising to £191,300. Assuming duloxetine replaces gabapentin, the net saving to the NHS would be £20,000 in 2006, rising to £384,000 in 2010.

Guidelines and protocols

The November 2001 SIGN publication number 55: management of diabetes, recommends tricyclic antidepressants as first line therapy in painful diabetic neuropathy. Gabapentin is also recommended as a treatment for this condition and is associated with fewer side effects than tricyclic antidepressants and older anticonvulsants. Topical capsaicin should be considered for the relief of localised neuropathic pain.

The July 2004 NICE clinical guideline 15: diagnosis and management of type 1 diabetes, recommends the use of simple analgesics (paracetamol, aspirin) and local measures (bed cradles) initially. Where these fail a low- to medium-dose of tricyclic antidepressant should be trialled. If this fails, gabapentin should be started and titrated to at least 1800mg daily if possible. If this is unsuccessful, carbamazepine and phenytoin should be considered. Where chronic pain continues to persist, opioid analgesia and referral to pain management services should be considered.

Additional information

After review of a resubmission, SMC issued advice in July 2005 that pregabalin (Lyrica®) for the treatment of peripheral neuropathic pain in adults is not recommended for use within NHS Scotland. The comparative dinical and cost effectiveness have not been demonstrated.

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.

This assessment is based on data submitted by the applicant company up to and including 15 August 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission.

Goldstein DJ, Lu Y, Detke MJ et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 2005; 116: 109-118

Raskin J, Pritchett YL, Wang F et al. A double-blind, randomized multicentre trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Medicine 2005; 6: 346-356

Wernicke JF, Lu Y, D'Souza DN et al. Duloxetine at doses of 60mg QD and 60mg BID is effective treatment of diabetic neuropathic pain. Poster presented at Am Acad Neurol, San Francisco 2004.

Raskin J, Smith TR, Wong K, et al. Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. J Palliat Med 2006; 9:29-40.

Wernicke JF, Rosen A, Lu Y et al. The safety of duloxetine in the long-term treatment of diabetic neuropathic pain. Poster presented at CINP, Paris 2004.