



**North East Treatment
Advisory Group**

**Agomelatine
(Valdoxan®)
in the management
of depression**

William Horsley
Lead Pharmacist for NETAG
September 2009

Summary

- Agomelatine is a new first-in-class antidepressant with a novel mode of action at melatonin and serotonin receptors. It is licensed for the treatment of major depressive episodes with minimum treatment duration of 24 weeks at a standard dose of 25 mg daily, or a higher dose of 50 mg daily.
- Agomelatine has demonstrated efficacy in several placebo-controlled studies. It has also demonstrated efficacy in short-term active comparator studies including one with 24 weeks of treatment follow-up. The evidence indicates that it is about as effective as existing treatment options. Nearly one quarter of patients eventually require the higher dose of agomelatine. There is scant evidence for use in older patients (age ≥ 65 years).
- Evidence regarding the safety and side-effect profile of agomelatine indicates a similar incidence of adverse effects to other commonly used antidepressants. It is associated with a low incidence of weight gain. Some active-comparator studies have demonstrated a lower incidence of specific treatment-emergent effects such as sleep disturbances and sexual dysfunction with agomelatine compared with other commonly used antidepressants.
- Agomelatine requires regular monitoring of liver function with attendant impact on healthcare resources, patients, and costs.
- Agomelatine is one of the most costly antidepressants available. The mean cost of one month's treatment with agomelatine is about £48. This compares with less than £5 per month for many commonly used antidepressants. Cost-effectiveness appears to improve as agomelatine is placed further down treatment algorithms. It is unlikely to prove cost-effective as a first- or second-line treatment option for the majority of eligible patients.

Introduction and Background

The management of depression is a significant burden on the NHS and is now one of the most common presenting indications in primary care. Within NHS North East during 2008-9 nearly £15 million was spent on antidepressant and related drugs within primary care alone, although not all use will have been indicated for depression.¹ The National Institute for Health and Clinical Excellence issued guidance in 2004 concerning the management of depression in adults with an update planned for publication in October 2009.^{2,3} The mainstay of pharmacological treatment of depression is use of a selective serotonin receptor inhibitor (SSRI). There are some drugs within this class that have good safety records, a substantial evidence base demonstrating benefit, and are available generically at low cost.^{2,3}

There are many different drugs available for treating depression, although most prescribing is restricted to a handful of drugs such as the SSRIs (fluoxetine, paroxetine, sertraline, and citalopram) and to a lesser extent an older class of drugs known as tricyclic antidepressants (TCAs) typified by amitriptyline, dosulepin, and lofepramine. Other drugs that are commonly used, but usually subsequent to use of a TCA or a SSRI, include those with serotonergic and noradrenergic properties such as mirtazapine and venlafaxine. Current NICE guidance recommends using a SSRI for first-line treatment of moderate to severe depression. The same guidance recommends a multitude of drug treatments if a second-line treatment is required (e.g. due to ineffective or non-tolerated first-line option) but emphasises use of an alternative SSRI or mirtazapine. Venlafaxine is considered a suitable second-line option 'especially for more severe depression'.²

Treatment-resistant depression is defined as failure to respond to an adequate trial of two or more antidepressants. Recommended options for treatment-resistant depression include a range of different drugs and drug combinations, combined with psychological therapy.²

The most recent update of NICE guidance for the treatment of depression in adults advises that second-line treatment options should be a different SSRI or a 'better tolerated newer-generation antidepressant'. Recommended subsequent treatment options (i.e. third-line or later) should be 'of a different pharmacological class that may be less well tolerated, for example venlafaxine, a TCA or a monoamine oxidase inhibitor'.³

Agomelatine is a first-in-class antidepressant with agonistic activity at melatonin receptors and antagonistic actions at certain serotonin receptors within the central nervous system. In addition, the activity at serotonin receptors appears to enhance levels of dopamine and noradrenaline in the frontal cortex.⁴

Agomelatine (Valdoxan®▼, Servier) has been available in the UK since June 2009. It is licensed for the treatment of episodes of major depressive disorder (MDD or 'depression') in adults and is available as a 25 mg tablet with the usual dose being one tablet daily. A higher daily dose of 50 mg may be indicated if symptoms have not improved after two weeks of treatment with the lower dose.⁵

Neither current NICE guidelines, nor the 2009 update, include consideration of agomelatine.^{2,3}

A major depressive episode is defined by the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as at least two weeks of depressed mood or loss of interest in usual activities, accompanied by at least four additional symptoms of depression such as; disturbed sleep, lethargy or apathy, poor concentration, inattention, indecisiveness, or suicidal ideation.⁶

The North East Treatment Advisory Group has been requested by a member specialist mental health trusts to conduct an appraisal of, and issue a treatment recommendation for, the use of agomelatine within its product license.

Clinical Evidence

Agomelatine has been widely studied in short and longer-term studies including a number of active-comparator studies. Only evidence pertinent to the licensed indication is considered within this report.

A commonly reported outcome is the Hamilton Rating Scale for Depression (HAMD) score. There is no evidence regarding what constitutes a clinically meaningful difference in HAMD score although NICE consider a 'between-group difference' of ≥ 3 points as the criterion for clinical significance.²

Common recruitment criteria included a diagnosis of MDD as per DSM-IV criteria and HAMD score ≥ 22 .

Short-term placebo-controlled studies

Three randomised, double-blind, placebo-controlled studies (combined $n = 1,171$), were undertaken to assess the short-term (six to eight weeks) efficacy of agomelatine.⁷⁻⁹ Compared with placebo, treatment doses of agomelatine produced a significantly greater reduction in HAMD scores relative to baseline.

Pooled data from these studies ($n = 721$) demonstrated a between group difference in final HAMD score of 2.86 ($p < 0.001$) in favour of agomelatine (all patients had baseline HAMD score ≥ 22). In subgroups with more severe depression defined by baseline HAMD ≥ 25 and HAMD ≥ 30 the difference was 3.00 ($p < 0.001$) and 4.53 ($p = 0.001$) respectively.¹⁰

Active comparator studies

There are limited published data comparing agomelatine with currently available antidepressants although abstract and unpublished data is also available. Two short-term studies of between six and 12 weeks duration compared agomelatine 25 to 50 mg daily with venlafaxine 75 to 150 mg daily. Although efficacy outcomes were not the primary focus of the studies, they did not demonstrate a significant difference between treatments with respect to changes in HAMD score.¹¹⁻¹²

Longer-term (≤ 24 weeks) outcome data concerning agomelatine versus venlafaxine is also available¹³ and originates from one of the above studies.¹¹ This demonstrates that patients treated with agomelatine showed a higher response rate (defined as $> 50\%$ reduction in HAMD score from baseline) compared with venlafaxine modified-release (70% vs. 62%, 'p' not stated).

Agomelatine 25 to 50 mg has also been compared with sertraline 50 to 100 mg in a six-week study. The difference in HAMD score changes between baseline and week six was 1.68 in favour of agomelatine ($p = 0.031$).¹⁴ TEXT REMOVED TO MAINTAIN CONFIDENTIALITY¹⁵

Agomelatine 25 to 50 mg has also been compared with fluoxetine 20 to 40 mg daily in an eight-week study in severely depressed patients with a HAMD score ≥ 25 ($n = 515$). TEXT REMOVED TO MAINTAIN CONFIDENTIALITY.¹⁵

None of the comparative studies used maximum licensed doses of the comparator drugs, which is up to 375 mg daily with venlafaxine, up to 60 mg daily with fluoxetine, and up to 200 mg daily with sertraline.¹⁶ Note that these maximum doses are uncommon in practice.

Longer-term placebo-controlled studies

Two, currently unpublished, placebo-controlled studies have evaluated the efficacy of agomelatine in the prevention of relapse of depression. Patients had recurrent depression (DSM-IV criteria) and a HAMD score of ≥ 22 .^{17,18}

In the first study responders were defined as those with HAMD ≤ 10 ($n = 339$) after eight to ten weeks of open-label treatment with agomelatine 25 to 50 mg daily ($n = 492$). Responders then entered a ten-month double-blind phase. The results demonstrated a significantly lower rate of relapse for patients treated with agomelatine compared with placebo (23.9% vs. 49.9%, $p < 0.0001$).^{18,19}

In the second study patients defined as responders after eight to ten weeks of open-label agomelatine 25 mg daily entered a 26-week double-blind phase. No significant difference on relapse rate was observed between agomelatine and placebo. However an 18-week extension phase investigating patients with severe depression (HAMD > 25 , $n = 169$) did identify a significantly lower relapse rate in favour of agomelatine (21% vs. 31% $p = 0.046$).^{17,19}

Summary of the clinical evidence

Agomelatine has been evaluated in a number of different studies although only a few have been published in peer reviewed journals. It has demonstrated efficacy compared with placebo and commonly used active comparators (specifically fluoxetine, sertraline, and venlafaxine) over the short and longer-term. The evidence indicates it is of equivalent efficacy to these drugs and that it maintains a significant clinical improvement for up to 24 weeks. It is worth noting that none of the active-comparator studies used maximum doses of the comparator drug

which may have introduced bias in favour of agomelatine. It should also be noted that efficacy was not the primary outcome measure in some of the active-comparator studies.

Much of the evidence is derived from studies of less than 24 weeks duration whereas the minimum recommended duration of treatment stipulated for agomelatine is 24 weeks. In common with use of other antidepressants, the greatest effects are often seen with the most severely depressed patients.

There is very little evidence relating to the use of agomelatine in older patients (age > 65 years). The product data sheet states "Efficacy has not been clearly demonstrated in the elderly (≥ 65 years). Therefore, caution should be exercised when prescribing Valdoxan® to these patients."⁵

Safety

Indirect comparisons of the overall incidence of adverse effects indicate comparable rates with other commonly used antidepressant drugs. The most common effects from short term studies were headache, nausea, dizziness, and dry mouth. Adverse events occurring at a significantly higher frequency with agomelatine than placebo in short-term studies were dizziness (5.5% vs. 3.1%), paraesthesia (0.9% vs. 0.1%), and blurred vision (0.6% vs. none). In longer-term placebo studies the corresponding effects were insomnia (2.5% vs. 0.7%) and sinusitis (1.4% vs. none).¹⁷

Some of the active-comparator studies were specifically designed to assess the development of treatment emergent effects. These short-term studies have demonstrated that agomelatine:

- Produces less discontinuation symptoms than paroxetine following discontinuation of treatment.²⁰
- Produces less treatment-emergent sexual dysfunction than venlafaxine.^{11,12}
- Results in greater improvements in sleep and related symptoms than sertraline.²¹

Weight gain appeared to be an uncommon adverse effect with an incidence estimated at 1% in patients treated for one year.¹⁷ Weight gain is a recognised side effect with some antidepressants, particularly TCAs and mirtazapine.²²

A non-significantly higher incidence of dose-related elevated liver function test (LFT) results, specifically serum transaminases > 3 times the upper limit of normal, were observed in 1.0 to 1.4% of agomelatine patients vs. 0.7% with placebo.¹⁷ Consequently it is a condition of treatment that LFTs should be performed for all patients at initiation of treatment and then periodically after around six, 12 and 24 weeks, and thereafter when clinically indicated.^{5,17}

Agomelatine is contraindicated for use with potent CYP1A2 inhibitors such as ciprofloxacin, and in patients with hepatic impairment.⁵ There are limited data

on the use of agomelatine in patients aged under 18 or over 65 years, and it should not be used for elderly depressed patients with dementia.^{5,17}

A specific project funded by Servier has been established to collect follow-up data on the use of agomelatine for depression. The project, known as NEVADA, is endorsed by the Mental Health Research Network, and by association has been adopted into the NHS National Institute for Health Research clinical studies portfolio. A senior mental health clinician within NHS North East is a member of the steering committee for the project. Servier will only have access to national outcome and adverse event data, and only to ensure compliance with regulatory functions. The system is computer based and participation is optional.²³

Economic analysis

Agomelatine is available in packs of 28 tablets at £38.53 per pack. A meta-analysis identified that about one quarter of patients require the higher dose of 50 mg daily,^{19,24} which would cost £77.06 per 28 days. The weighted mean cost per 28 days is therefore about £48.

The marketing authorisation holder has provided an evidence-based cost utility analysis derived from their submission to the Scottish Medicines Consortium.¹⁵ The key assumptions within the standard model are:

- Treatment duration of 24 weeks, with a proportion ceasing treatment at a six-week review. Treatment duration > 24 weeks is not modelled.
- 15% of patients require the maximum daily dose of 50 mg during weeks 3 to 24.
- The model includes all reasonable costs such as: LFTs, outpatient visits, GP visits, agomelatine and other drug costs.

Three scenarios are estimated: (a) substitution for venlafaxine with subsequent use of mirtazapine for non-responders, (b) substitution for venlafaxine after all other treatment options have been considered, and (c) use as an alternative to nil treatment/supportive care.

The analyses with respect to venlafaxine (scenarios a & b) use results derived from a single study that was not designed to assess efficacy as the primary outcome.¹¹ The model also uses a cost for venlafaxine that may not accurately reflect the costs faced within NHS North East. For example, it assumes the use of venlafaxine tablets which are less costly than the most commonly used presentation within NHS North East (modified release capsules). This arises due to the design of the relevant study.¹¹ Additionally, the maximal dose of venlafaxine used in the relevant study was 150 mg whereas in practice higher and more costly doses may be used. These factors probably lead to bias against agomelatine as they will result in apparently lower offset costs than might be expected. However, the model uses TEXT REMOVED TO MAINTAIN CONFIDENTIALITY and also assumes that only 15% of patients require treatment with the higher dose whereas an unpublished meta-analysis found that

24% require the higher dose.¹¹ These factors will lead to bias in favour of agomelatine.

Similar issues are present with the modelled use of mirtazapine as a subsequent therapy, where the rates of use of specific doses vary to those used within NHS North East, and the costs are greater than current values. These will bias in favour of agomelatine by overestimating the offset costs.

A condition on the use of agomelatine is that liver function tests (LFTs) are performed at baseline, 6, 12 and 24 weeks as a minimum. There are obvious cost implications attached to this requirement. It is estimated that a standard LFT costs about £4.²⁵ If all four tests are performed for all patients over a 24 week period this will add £16 to a single 24-week treatment course, or about an extra 6% to 7% on top of drug acquisition costs. The economic model uses a cost of £2.84 per LFT. This value appears to originate from the costs of pathology tests as apply to acute medical trusts and not necessarily those that apply in primary care or within a specialist mental health trust. The net effect is small but will bias in favour of agomelatine by underestimating this associated cost.

Other costs within the model are referenced against independent sources and appear reasonable. Costs for acute care have not been estimated using the Department of Health payment by results tariff, which specifically excludes adult mental health, and therefore may not reflect local costs. For example the cost per unscheduled hospital visit (i.e. A&E visit) is estimated at £98, compared to a current tariff price of between £59 and £109. The net effect will be small.

On the basis of these assumptions the incremental cost-effectiveness ratio per quality adjusted life year for scenario (a) is £X, for scenario (b) it is £Y, and for scenario (c) it is £Z. (ACTUAL VALUES REMOVED TO MAINTAIN CONFIDENTIALITY) The actual values should be interpreted cautiously for the reasons previously outlined. A clear trend is present where the cost-effectiveness increases as the new treatment, agomelatine, is reserved for ever more resistant or severe patients, as implied by the scenarios.

The recommended minimum duration of treatment with agomelatine is 24 weeks which does not differ from other antidepressant drugs. The cost for a 24-week course of treatment with agomelatine, assuming that about one quarter of patients will receive the higher dose from week 5, is £280 (£218) per patient, plus £16 for LFTs.

Agomelatine as an alternative to venlafaxine

As suggested by the economic model scenarios, agomelatine may be considered as an alternative treatment to venlafaxine. The total number of days of venlafaxine prescribed within NHS North East primary care in 2008-09 cannot be reliably estimated from prescription data because, despite standard doses, some patients may take a greater number of tablets/capsules to obtain higher treatment doses. Total expenditure on venlafaxine was £5.37 million.

Using an average daily quantity of 100 mg, ²⁶ there were about 5.36 million days treatment with venlafaxine dispensed in this period. If agomelatine was substituted for 10% of this use it would represent 536,000 days treatment at a cost of about £919,000. Offset against this would be the cost of venlafaxine yielding a net cost of about £382,000. This is equivalent to 3,190 patients all receiving treatment for 24 weeks. Venlafaxine is associated with some monitoring requirements, especially at higher doses, and it is assumed that the cost of these is balanced by the cost of LFTs required with agomelatine.

These figures are for indicative purposes only and are not evidence based. It should be noted that venlafaxine is not only licensed for the treatment of depression but also anxiety disorders and so the estimated value will likely overestimate the use of venlafaxine for treating depression.

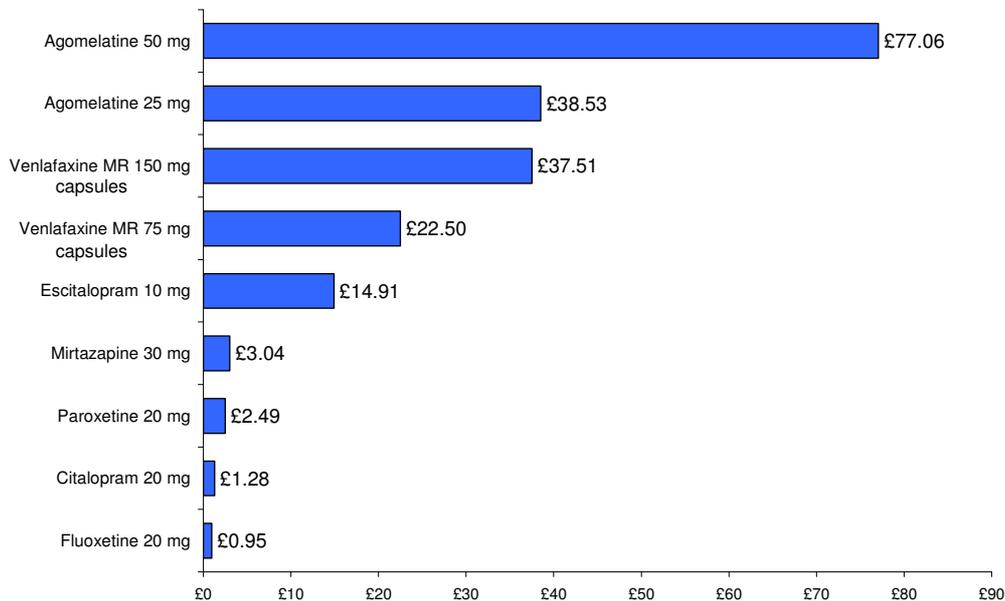
Venlafaxine has fallen in price substantially since January 2009 when generic versions became available. The cost of venlafaxine is expected to fall further as the reimbursement price better reflects actual wholesale prices.

The 10% rate of substitution has been arbitrarily selected and does not take into account potential differences in duration of treatments.

Agomelatine as an alternative to mirtazapine

Alternatively, agomelatine could be considered as a substitute for mirtazapine, which is also often used as a second-line or subsequent treatment. Based on standard dose frequencies, within NHS North East primary care 2008-09 there were 437,000 days treatment dispensed at a cost of about £1.9 million. If 10% of this was substituted for agomelatine the cost would be £749,000 for agomelatine with an offset cost of £190,000 yielding a net cost of £559,000. Mirtazapine is not associated with any specific monitoring requirements, therefore an additional cost with agomelatine would be the cost of LFTs. This is crudely estimated at £42,000 based on all patients completing a 24-week treatment period. This estimate is equivalent to 2,600 patients.

Fig 1. Comparison chart of cost of 28 days treatment with agomelatine and commonly used antidepressants²⁷



Points to consider

Agomelatine is the first in a new class of melatonergic antidepressants. Currently there are more than 20 different antidepressants from several pharmacological classes available in the UK.

Agomelatine appears to be an effective treatment for moderate to severe depression. Short-term randomised placebo-controlled and active comparator studies suggest comparable efficacy to currently licensed antidepressants. There is little evidence for use of agomelatine in older patients (age \geq 65 years).

The safety of agomelatine has been established in relatively short duration studies. Separate studies have demonstrated a lower incidence of some specific treatment-emergent effects such as sexual dysfunction and sleep disturbances compared with sertraline and venlafaxine.

Patients being treated with agomelatine must undergo regular liver function tests due to a small increased risk of raised liver enzymes.

Agomelatine is one of the most costly antidepressants available based on typical daily treatment costs.²⁸ Given the large range of effective treatment options already available at low cost, agomelatine is unlikely to be cost-effective unless targeted at particular patient groups who may benefit most from its specific pharmacological profile. The current evidence base does not allow these patients to be reliably identified but indicates it may be those who cannot tolerate particular effects related to other treatments.

Author's declaration

The author has attended two separate educational training days delivered by a third party academic, which were entirely sponsored by Servier Laboratories.

References

1. Data provided by the Regional Drug and Therapeutics Centre (Newcastle).
2. National Institute for Health and Clinical Excellence. Depression in adults (update) – Depression: the treatment and management of depression in adults. Final draft, July 2009
3. National Institute for Health and Clinical Excellence. Depression: Management of depression in primary and secondary care. National Clinical Practice Guideline Number 23. December 2004 (updated 2007)
4. San L, Arranz B. Agomelatine: A novel mechanism of antidepressant action involving the melatonergic and the serotonergic system. *European Psychiatry* 2008;23:396-402
5. Summary of product characteristics. Agomelatine (Valdoxan®, Servier). June 2009
6. <http://allpsych.com/disorders/mood/majordepression.html>
7. Kennedy S, Elmsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *European Neuropsychopharmacology* 2006;16:93-100
8. Loo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatonergic agonist and selective 5-HT_{2C} antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *International Clinical Psychopharmacology* 2002;17:239-47
9. Olie J, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT_{2C} antagonistic properties, in major depressive disorder. *International Journal Neuropsychopharmacology* 2007;10:661-73
10. Montgomery S, Kasper S. Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. *International Clinical Psychopharmacology* 2007;22:283-91
11. Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: Randomized, double-blind comparison with venlafaxine. *Journal of Clinical Psychiatry* 2007;68(11):1723-32
12. Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *Journal of Clinical Psychopharmacology* 2008;28(3):329-33
13. Kennedy SH. Efficacy of agomelatine from treatment initiation to treatment completion. Poster abstract presented at the 21st ECNP Congress, Spain, August 2008
14. Kasper S, Laigle L, Bayle F. Superior antidepressant efficacy of agomelatine vs sertraline: a randomized, double-blind study. Poster abstract presented at the 21st ECNP Congress, Spain, August 2008.
15. Unpublished data provided by Servier Pharmaceuticals, August-September 2009
16. British National Formulary. 57th edition. Accessed online via www.bnf.org
17. European Medicines Agency. CHMP assessment report for Valdoxan. Document reference EMEA/655251/2008, London, November 2008
18. Goodwin G, Rouillon F, Emsley R. Long-term treatment with agomelatine: prevention of relapse in patients with major depressive disorder over 10 months. Poster abstract presented at the 21st ECNP Congress, Spain, August 2008.

19. Denby A. Agomelatine APC/DTC briefing document. London New Drugs Group June 2009
20. Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled, discontinuation study. *International Clinical Psychopharmacology* 2004;19:271-280
21. Kasper S, Wulff K, Laigle L, Bayle F. Effect of agomelatine on rest-activity cycle in patients with major depressive disorder compared to sertraline. Poster abstract presented at the 26th CINP congress, Munich, July 2008
22. Fava M. Weight gain and antipressants. *Journal of Clinical Psychiatry* 2000;61(S11):37-41
23. Taylor D, NEVADA Steering Committee. The rationale and design of a UK database to gather naturalistic data on agomelatine and to audit its use in the treatment of Major Depressive Episodes (MDE). *Insights In Healthcare (Itd)* 2008
24. Personal communication with Servier, August 2009
25. Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, Rosenberg W. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). *Health Technology Assessment* 2009;13:25
26. NHS Information Centre www.ic.nhs.uk/webfiles/Services/PSU/adqs_2007_08.pdf
27. NHS Dictionary of medicines and devices, September 2009 www.dmd.nhs.uk
28. Regional Drug and Therapeutics Centre. Cost comparison charts. July 2009. www.nyrdtc.nhs.uk