Acetylcholinesterase Inhibitors

Maximising benefits to the Surrey healthcare economy from the loss of exclusivity of donepezil, galantamine and rivastigmine in 2012-13

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1. PURPOSE OF THE REVIEW

The acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine will lose their exclusivity in 2012 enabling generic versions to enter the market. Current prescribing patterns in primary care suggest that significant "windfall" savings will be made in 2012-13 and subsequent years.

NICE Technology Appraisal 217 states that *"If prescribing an AChE inhibitor treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles".*

This review explores the possible scenarios relating to the change in the market for these drugs and makes recommendations to enable patients to access these drugs in a cost-effective way for the Surrey health economy.

2. BACKGROUND[1]

The Intellectual Property Office describes a patent as 'a form of Intellectual Property that protects new inventions and covers how things work, what they do, how they do it, what they are made of, and how they are made. It gives the owner the right to prevent others from making, using, importing or selling the invention without permission'. In the UK, patents' legislation is embodied in the 1977 Patents Act. Patents applying to pharmaceuticals cover many aspects, including their manufacture, formulation and, in some cases, their use. Once a patent on a drug has expired, especially that relating to the processes of its manufacture, generic versions of the drug can be manufactured and marketed. The basic patent is rarely the only protection involved and other process, chemical form, or formulation patents may be relevant. These may all extend the effective patent life of a product. The basic expiry date can only be taken as a guide to the earliest possible date for any generic form to appear.

[1] Drug patents: which will expire in 2012 and 2013?, prepared by UK Medicines Information pharmacists for NHS healthcare professionals, 23 March 2012 http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Q--A/Drug-patents-which-will-expire-in-2009-and-2010/ (accessed 10 April 2012)

Patents on specific formulations or chemical variations, for example new salts, can delay the introduction of generic brands.

A Supplementary Protection Certificate (SPC) is a mechanism to guarantee a certain marketing exclusivity period for medicines throughout the European Union (EU), to allow for the extended development period they require. Current patents in the EU are valid for 20 years; an SPC applies from the date of first marketing of a product within the EU, and extends the effective patent life for up to 5 years, to allow up to a maximum of 15 years exclusivity.

Extensions to SPCs arising from paediatric trials: On 26 January 2007, regulation (EC) No. 1901/2006 came into force. This Regulation sets out the new legislative framework to promote the development of medicinal products for use in the paediatric population. Amongst its incentives is the possibility of an extension to the duration of a SPC covering a marketed medicinal product. Before this regulation came into force, the maximum duration of an SPC was five years. Now, under the provisions of the new Regulation, an SPC covering a product may be extended (beyond the term that it would otherwise be afforded) by a period of six months. This extension of term applies to all of the authorised indications for the product (including the non-paediatric indications).

3. CURRENT RECOMMENDED PRACTICE

NICE TA 217 (March 2011) 'Donepezil, galantamine, rivastigmine (anticholinesterase or AChE inhibitors) and memantine for the treatment of Alzheimer's disease' makes the following recommendations:

- Donepezil, galantamine and rivastigmine are now recommended as options for managing mild as well as moderate Alzheimer's disease, **and**
- Memantine is now recommended as
    - an option for managing moderate Alzheimer's disease for people who cannot take AChE inhibitors, and
    - as an option for managing severe Alzheimer's disease.
- Specialists should initiate treatment. Prescribing can continue in primary care under shared care agreements. A shared care agreement for memantine is under development and the existing agreement for AChe Inhibitors is being updated to conform with latest NICE guidance by SABP (APC August 2011).
- If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest **acquisition cost**.

4. CURRENT EXPENDITURE AND MARKET SHARE IN NHS SURREY (PRIMARY CARE)

Shared care has been in place for a number of years in NHS Surrey so a significant amount of prescribing of AChE inhibitors occurs in primary care. Surrey and Borders Partnership Mental Health Trust and other acute trusts also incur expenditure on these drugs but these costs are not shown here (see Table 1).

Table 1: Primary Prescribing of AChE Inhibitors in NHS Surrey February 2011 – January 2012

Drug/Class	Indication	Expenditure Feb 2011 – Jan 2012	Market share (items)
Donepezil (Aricept®)	Mild to moderate dementia in Alzheimer's disease.	£1,974,103	65.3%
Galantamine (Reminyl®)	Mild to moderate dementia in Alzheimer's disease.	£420,887	15.0%
Rivastigmine (Exelon®)	Mild to moderate dementia in Alzheimer's disease. Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease (excludes patches).	£172,904	12.2%
Memantine (Ebixa®)	Treatment of patients with moderate to severe Alzheimer's disease.	£172,904	7.5%
Total Spend 12 months (February 2011 – January 2012)		**£2,937,547**	

5. CLINICAL EFFECTIVENESS

The three AChE inhibitors are all indicated for mild to moderate dementia in Alzheimer's disease; rivastigmine is also indicated in Parkinson's disease. The evidence to support the use of these drugs relates to their cognitive enhancement. NICE concluded that there was insufficient evidence to differentiate between the AChE inhibitors in terms of cost effectiveness and recommends that treatment should normally be started with the drug with the lowest acquisition cost.

6. SAFETY (refer to SPC of each drug for full details)

All AChE Inhibitors need to be used with caution or avoided with hepatic impairment. All need to be used with caution or avoided in renal impairment except donepezil.

***Donepezil*:**

- Contra-indications: hypersensitivity to donepezil.
- Cautions: Sick-sinus syndrome, other supraventricular conduction abnormalities, susceptible to peptic ulcer, asthma, COPD, hepatic impairment.

Galantamine:

- Contra-indications: hypersensitivity to galantamine. Renal impairment (CrCl <9ml/min). Significant hepatic dysfunction.
- Cautions: Cardiac disease (including sick-sinus syndrome, other supraventricular conduction abnormalities, unstable angina, congestive heart failure) electrolyte disturbances, susceptible to peptic ulcer, asthma, COPD, hepatic impairment, urinary obstruction, gastrointestinal obstruction.

***Rivastigmine*:**

- Contra-indications: hypersensitivity to rivastigmine, severe liver impairment.

- Cautions: sick-sinus syndrome, asthma, COPD, seizures, bladder obstruction, gastric or duodenal ulcers, hepatic impairment, renal impairment. Monitor body weight (weight loss may occur)

7. ADMINISTRATION

- All AChE inhibitors are available as standard immediate release capsules/tablets. Donepezil is taken once daily; rivastigmine and galantamine are twice daily doses.
- Rivastigmine and Galantamine are available as oral solutions
- Galantamine is available as a prolonged release tablets (once daily formulation)
- Rivastigmine is available as a patch which is applied each day. The patches are associated with fewer gastro-intestinal side effects than the oral formulation.

8. PATENT EXPIRY DATES

Table 2: Patent Expiry dates for AChE Inhibitors and memanatine

Drug	Patent Expiry date (from UKMi database)	Comments
Galantamine (Reminyl)	15/01/2012	First generics became available in February 2012. Initial prices of standard and extended release preparations 15% lower than Reminyl®
Donepezil (Aricept)	13/02/2012	A number of generics became available in February 2012. Initial prices of 2 manufacturers are 80% lower than Aricept® for both standard and orodispersible preparations
Rivastigmine (Exelon)	30/07/2012	Not yet available
Memantine (Ebixa)	13/04/2014	

9. COST MODEL FOLLOWING LOSS OF EXCLUSIVITY

a) Considerations

1. **Standard release formulations** - Experience in recent years from other branded drugs that have lost their exclusivity suggests that generic prices in primary care have typically dropped to 28% (72% discount) of the original price in the first quarter after patent expiry with a drop to around 7% (93% discount) at 18 months.
2. **Orodispersible formulations –** there is limited experience with these formulations in relation to generic price decreases. Reductions are likely to be related to the number of generic manufacturers marketing this formulation. Initial prices of 2 manufacturers are 80% lower than Aricept® for both standard and orodispersible preparations of donepezil.
3. **Modified release formulations –** although generic versions of modified release formulations may become available, there is no guarantee that prices will fall as significantly as the standard release formulations. Experience with drugs such as

venlafaxine MR suggests that reductions in acquisition costs of around 50% may be feasible. One of the first galantamine XL formulations to be launched has been priced at 15% lower than Reminyl® XL

4. **Oral Solutions –** due to low item volumes these do not tend to drop in price as quickly as standard release preparations. There is currently no indication of potential costs of generic versions.
5. **Patches** - currently there have been no applications at MHRA for generic rivastigmine patches

b) Assumptions

Table 3 below indicates the estimated expenditure of AChE Inhibitors in NHS Surrey for 2011-2015. The following assumptions have been made:

1. Reduction in standard release and orodispersible formulation as follows:
   - 50% reduction 3-5 months post patent expiry
   - 70% reduction 6-8 months post patent expiry
   - 85% reduction 9-11 months post patent expiry
   - 90% reduction 12 months post patent expiry
2. Reduction in cost of modified release preparations by 20% of current costs (estimated average reduction as some patients may remain on original branded product)
3. Reduction in cost of liquid preparations by 20% of current costs
4. 90% conversion of currently prescribed branded standard release preparations to generic
5. 8% growth in the number of items prescribed

Table 3: Estimated expenditure of AChE Inhibitors in NHS Surrey for 2011-2015.

Year	Total Costs	Standard release formulation	Modified release formulations	Liquid formulations	Branded Preparations (standard release)	Patches
2011-12	£2,764,643	£1,957,363	£375,398	£23,359	£170,011	£238,512
2012-13	£1,765,684	£1,041,322	£353,570	£24,496	£95,616	£250,679
2013-14	£916,000	£231,523	£350,197	£26,191	£36,768	£271,343
2014-15	£982,000	£241,035	£379,065	£28,320	£39,700	£293,710

Based on the assumptions above, by 2013-14 “windfall” savings on AChE inhibitors can be expected to reach around £2 million per year compared to current costs. Currently, standard release preparations represent 71% of total expenditure whereas by 2013-14 this is likely to drop to around 25% or less. The remaining 75% will represent expenditure on modified release preparations, liquids, patches and any outstanding brand prescribing.

10. BUDGETARY IMPACT

If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles

Table 4: AChE Inhibitor formulations, current annual costs and estimated annual costs 12 months after generic availability

Drug	Formulation	Once Daily (current annual cost)	Twice daily (current annual cost)	Estimated Annual Cost 12 months after generic availability*
Donepezil 5mg	Dispersible / standard tablets	£777		£54
Donepezil 10 mg	Dispersible / standard tablets	£1,091		£76
Galantamine 8mg	Standard tablets		£891	£62
Galantamine 12mg	Standard tablets		£1,095	£77
Galantamine 16mg XL	Modified-release capsules	£843		£421
Galantamine 24mg XL	Modified-release capsules	£1,040		£520
Galantamine 20mg/5ml	Oral solution		£1752 – £2,628	£876 - £1,314
Rivastigmine 3mg, 4.5mg, 6mg	Standard release capsules		£861	£60
Rivastigmine 4.6 mg/ 24 hours or 9.5mg/24hours	Transdermal patches	£945		£945
Rivastigmine 2mg/ml	Oral solution sugar free		£898 – £1,796	£449 - £898

*Standard release / orodispersible estimated at 93% cost reduction; modified-release oral solution estimated at 50% cost-reduction

5. Conclusions and Recommendations

Options to consider for the use of AChE inhibitors for mild to moderate Alzheimer's Disease include:

	Recommendation	Rationale
1	All solid dose / liquid formulations of AChE inhibitors should be prescribed generically.	To obtain the lowest acquisition cost per NICE TA217 once patents expire.
2	Oral solid dose formulations should be prescribed as first line treatment unless there are patient factors that make these unsuitable*	Experience from many other patent expiries suggests that these formulations fall in price more rapidly and to a greater extent than other formulations. It is reasonable to expect a 90%+ fall in price within 12 months
3	Donepezil orodispersible tablets should be considered as a suitable first line treatment for patients when there are difficulties in swallowing the solid dose formulations.	Generic versions already available and likely to be available at a low acquisition cost; once daily formulation
4	Rivastigmine oral solution 2mg/ml should be prescribed second line when donepezil orodispersible tablets cannot be tolerated or is unsuitable for the patient	Applications have been made to MHRA for a generic version
5	Galantamine oral solution 20mg/5ml should be prescribed third line where the other AChE inhibitors cannot be tolerated or are unsuitable.	No applications have yet been made to MHRA for a generic version
6	Prolonged-release galantamine should be considered when patients are unable to tolerate once daily formulations of donepezil and lack of adherence has been identified as a risk	Generic versions will be available but acquisition costs unlikely to fall to same level as oral dose formulations
7	Rivastigmine patches should be considered if patients are unable to tolerate other AChE inhibitors due to adverse gastro-intestinal effects.	No applications have yet been made to MHRA for a generic version

- The PCN may wish to consider if this should be more prescriptive, i.e, make donepezil 1st line with rivastigmine or galantamine as suitable alternatives if donepezil is not tolerated. The rationale for this decision includes:
    a) as the drug with the current highest market share it is likely that more generic suppliers will enter the market leading to a more rapid and greater fall in acquisition cost
    b) once daily formulation (compared to twice daily dose for galantamine and rivastigmine solid dose formulation)
    c) It is likely that the orodispersible formulation will be available at a similar acquisition cost

d) donepezil has a slightly safer profile than the other anticholinesterase inhibitors as it can be used in renal impairment

- The PCN may also wish to consider if there is scope to recommend a switch from formulations that will remain relatively highly priced to lower cost formulations. An additional reduction in expenditure of around £600,000 per annum could potentially be achieved although realistically some patients would need to remain on these preparations. Guidance from specialists in the care of dementia patients should be sought