NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA32; Multiple sclerosis - interferon beta and glatiramer acetate, TA127; Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis, and TA254; Fingolimod for the treatment of relapsing-remitting multiple sclerosis

This guidance was issued in: January 2002 (TA32); August 2007 (TA127); April 2012 (TA254).

The review date for TA127 had been set to coincide with the presentation of results from the SURPASS trial, which were anticipated in 2013. This study has now been terminated. The review of TA32 has previously been deferred and rescheduled to coincide with consideration of a review of TA127. A review decision on TA254 has also been scheduled to coincide with the review date of TA32.

1. Recommendation

A combined review of TA32, TA127 and TA254 should be planned into the NICE work programme.

That we consult on this proposal.

2. Original remit(s)

TA32: To appraise the clinical and cost effectiveness of beta interferon and glatiramer acetate (within their licensed indication) for the treatment of multiple sclerosis**.**

TA127: To appraise the clinical and cost effectiveness of natalizumab in its licensed indications for the treatment of multiple sclerosis, and to provide guidance to the NHS in England and Wales.

TA254: To appraise the clinical and cost effectiveness of fingolimod within its licensed indication for the treatment of relapsing-remitting multiple sclerosis.

3. Current guidance

TA32

1.1 On the balance of their clinical and cost effectiveness neither beta interferon nor glatiramer acetate is recommended for the treatment of multiple sclerosis (MS) in the NHS in England and Wales.

1.2 It is likely that patients currently receiving beta interferon or glatiramer acetate for MS, whether as routine therapy or part of a clinical trial, could suffer loss of

well being if their treatment is discontinued at a time they did not anticipate. Because of this, all NHS patients who are on therapy at the date of publication of this guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop, having regard to the criteria established for withdrawal from treatment in the Guidelines of the Association of British Neurologists published in January 2001. This also applies to all participating patients at the conclusion of a clinical trial (irrespective as to whether they had received placebo or active drug) and women whose therapy has been interrupted by pregnancy.

1.3 The Department of Health and the National Assembly for Wales are invited to consider the strategy outlined in Section 7.1 with a view to acquiring any or all of the medicines appraised for this guidance in a manner that could be considered to be cost effective.

TA127

1.1 Natalizumab is recommended as an option for the treatment only of rapidly evolving severe relapsing–remitting multiple sclerosis (RES). RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

1.2 People currently receiving natalizumab, but for whom treatment would not have been recommended according to section 1.1 of this guidance, should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

TA254

1.1 Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if:

- they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, and
- the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.

1.2 People currently receiving fingolimod whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

4. Rationale[1]

Interferon beta and glatiramer acetate are currently provided in the NHS through the multiple sclerosis risk-sharing scheme. This was set up in 2002 and involves detailed

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

monitoring of a cohort of patients to confirm the cost-effectiveness of these treatments. Preliminary data from the MS risk sharing scheme have already been published, and further data are likely to become available within the timeframe of a multiple technology appraisal. These data will be informative in estimating the clinical and cost effectiveness of the disease modifying drugs over several years.

Furthermore, there are ongoing appraisals of four new drugs for the treatment of relapsing-remitting multiple sclerosis - alemtuzumab, dimethyl fumarate, laquinimod and teriflunomide – in which beta interferon, glatiramer acetate, fingolimod and natalizumab are indentified as comparators (fingolimod and natalizumab are not comparators for dimethyl fumarate).

5. Implications for other guidance producing programmes

The Centre for Clinical Practice (CCP) welcomes the proposal. CCP is currently developing a full replacement for its 2003 guideline on multiple sclerosis (CG8). However, the scope of this work specifically excludes disease-modifying therapies, so that there will be no overlap with any current or planned technology appraisal guidance. The new clinical guideline will simply cross-refer to the current technology appraisal guidance on these drugs.

6. New evidence

The search strategy from the original assessment reports were re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from December 2009 (TA32), May 2010 (TA127) and the 15th April 2010 (TA254) onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

There are differences in the populations covered by the current marketing authorisations for fingolimod, natalizumab, interferon beta-1a and interferon beta-1b. Fingolimod and natalizumab are indicated for people with highly active relapsing remitting MS and the marketing authorisation for both drugs cover two populations in which there may be some overlap: patients with high disease activity despite treatment with a beta-interferon and patients with rapidly evolving severe relapsing remitting multiple sclerosis. Interferon beta-1a is indicated for people with relapsing remitting MS. Interferon beta-1b is indicated for people with relapsing remitting MS or secondary progressive MS. Glatiramer acetate is indicated for relapsing remitting MS in people who are ambulatory.

Since the publication of Technology Appraisal number 32 (TA32), interferon beta-1a, -1b and glatiramer acetate are now also indicated for people experiencing a single demyelinating event or well defined first clinical episode with high risk of developing clinically definite multiple sclerosis. In 2009 NICE received a referral to appraise interferon beta-1b, interferon beta-1a and glatiramer acetate for the treatment of single demyelinating event with clinically isolated syndrome, with a specific remit that it would be carried out alongside any future review of TA32. As TA32 has been on

the list of static guidance since the remit for clinically isolated syndrome was received this appraisal has effectively been suspended.

There have been no other changes to the marketing authorisations for interferon beta-1a, -1b, glatiramer acetate, natalizumab or fingolimod since Technology appraisals number 32,127 and 254 were published. The manufacturers of fingolimod may apply for an extension to the license to include people with primary progressive MS, a potential UK launch date for this extended license is Q4 2015. Natalizumab is being assessed in a clinical trial for its efficacy in secondary progressive MS, with the trial scheduled to complete in December 2014.

New treatments launched or in clinical trials since TA 32

Since the publication of TA 32 there is a new, proprietary interferon beta-1b, Extavia (Novartis Europharm Ltd) which received its license in 2009 and does not fall under the risk sharing scheme. The manufacturers of Rebif, one of the interferon beta-1a treatments assessed inTA32 have developed a new formulation of this product, which was designed to improve injection tolerability and reduce immunogenicity. The new formulation Rebif has gained marketing authorisation and was launched in 2007. A pegylated form of recombinant human interferon beta -1a is currently being assessed in a clinical trial for relapsing remitting MS. This trial is expected to complete in April 2013. This drug, BIIB-017 (Biogen Idec), was considered for appraisal as a single technology, however it was determined that it should be considered as part of this MTA review should it proceed. The manufacturers of BIIB-017 expect it to receive marketing authorisation in [redacted]. There is currently an ongoing trial of NU 100, a proprietary recombinant human interferon beta-1b in an aggregate free liquid formulation. The estimated completion date for this trial in December 2014.The drugs alemtuzumab, dimethyl fumarate, laquinod and teriflunamide are currently being appraised through the NICE single technology appraisal process.

The Risk Sharing Scheme

In 2007 it was decided that TA32 should stay on the static list until data emerges from the risk-sharing scheme developed by the Department of Health. This scheme is scheduled to run until 2015. In 2009 the 2 year outcomes of the clinical cohort receiving drugs covered by the risk sharing scheme with a historical comparator stated that it is too early to reach conclusions about the cost-effectiveness of interferon beta and glatiramer acetate from the first interim analysis (Boggild et al. 2009).

[redacted].

New trials of interferon beta-1a, -1b, glatiramer acetate and fingolimod

The BECOME study assessed interferon beta-1a compared with glatiramer acetate in 75 people over 2 years who had relapsing remitting multiple sclerosis or clinically isolated syndromes. The primary outcome was the number of combined active

lesions assessed using MRI. Secondary outcomes included clinical exacerbations. There were no differences between interferon beta-1a and glatiramer acetate in terms of MRI and clinical activity (Cadavid et al. 2009).

The BEYOND study compared 250 micrograms interferon beta-1b, 500 micrograms interferon beta-1b and glatiramer acetate in 2244 people randomised 2:2:1 to the two doses of interferon beta-1b and glatiramer acetate respectively (O'Connor et al. 2008; O'Connor et al. 2009). Participants were followed for up to 3.5 years. The primary outcome was relapse risk (new or recurrent neurological symptoms separated by at least 30 days from the preceding event or that lasted at least 24 hours). Safety and tolerability were also assessed. Although interferon beta-1b and glatiramer acetate had different adverse event profiles, the overall tolerability to both drugs was similar, as was the effectiveness.

The CombiRx trial assessed a combination of interferon beta-1a with glatiramer acetate compared to monotherapy of either treatment in 1008 people with relapsing MS, with at least 2 episodes of MS activity in the previous 3 years. The trial aimed to follow people for 3 years and the primary outcome was relapse rate (Lindsey et al. 2012). Data from this trial was presented at the Annual Meeting of the American Academy of Neurology 2012. For the risk of relapse outcome interferon beta-1a with glatiramer acetate combined was not superior to monotherapy; glatiramer acetate was superior to interferon beta-1a (CombiRX trialists 2012).

There is an ongoing trial of fingolimod compared with interferon beta-1b. The aim of this trial is to evaluate the effects of these treatments on slowing or reducing the progression of cognitive dysfunction in people with relapsing remitting multiple sclerosis after 18 months of treatment. The trial aims to enrol 150 people and the estimated date for final data collection for the primary outcome measure is in June 2014.

Observational studies of long term follow up

There are recent publications from the observational long term follow up of people who participated in pivotal trials of interferon beta, glatiramer acetate, natalizumab and fingolimod. These include a 15 year follow up of people exposed to treatment in MSCRG trial of the interferon beta-1a, Avonex (Bermel et al. 2009); analysis of the survival outcomes and cause of death of participants in the 21 years following the pivotal trial of the interferon beta-1b, Betaferon (Reder et al. 2012) follow up of the PRISMS trial which had assessed 2 doses of interferon beta-1a compared to placebo (Uitdehaag et al. 2011);a 15 year prospective open label study of glatiramer acetate (Ford et al. 2010); an ongoing open label, study (STRATA) currently in its long term extension phase to evaluate the safety and efficacy in 1094 people who had participated in the AFFIRM (natalizumab vs. placebo); SENTINEL (natalizumab with interferon beta vs. interferon beta alone) and GLANCE (natalizumab with glatiramer acetate vs. glatiramer acetate alone) trials and their extension phases over a further 5 years (Goodman et al. 2011). Data have been published from the TRANSFORMS extension study where people receiving fingolimod continued to take fingolimod, people on interferon beta switched to fingolimod for a further 2 years of follow up (Khatri et al. 2011).

New evidence for treatments used off-license in MS

A Cochrane systematic review of effects of the immunosuppressive drug azathioprine used in MS compared to placebo was published in 2007 (Casetta et al. 2007). In the updated search for this proposal paper results from a randomised control that compared azathioprine to a interferon beta in 150 people with relapsing remitting MS followed over 2 years has been published. The authors reported that in non-inferiority analysis azathioprine was associated with a similar annual relapse rate to interferon beta (Benedetti et al. 2012). Azathioprine is sometimes used off-license in the UK, but there are some concerns about its side effects. The NICE clinical guideline for multiple sclerosis, CG8, says that azathioprine should not be used unless there has been a full discussion and consideration of all the risks, its use will be evaluated preferably in a randomised or other prospective study, and it will be prescribed by an expert in the use of this medicine in MS. Azathioprine was not a listed comparator in TA32, 127 or 254.

Summary

Technology Appraisal 32 does not recommend interferon beta-1a, -1b or glatiramer acetate as cost effective treatment options. Only two year interim analyses are currently available from the Risk Sharing Scheme cohort, and it is unclear when further data will be published. The scheme is due to run until 2015. There have been further observational studies published on the long term outcomes of people exposed to interferon beta-1a, -1b and glatiramer acetate, which were a key uncertainty in TA32. However, future analyses from the Risk Sharing Scheme should be key to determine whether the uncertainties surrounding modelling both short and long term outcomes, experienced in TA32 can be overcome should an appraisal go ahead. There are no new data from randomised control trials of fingolimod or natalizumab. There are new proprietary interferon beta treatments available that are not covered by the risk sharing scheme and there is new data from randomised trials that have compared glatiramer acetate and interferon beta to each other and combination treatment. Following consultation it was determined that an appraisal of pegylated interferon beta, and an appraisal of glatiramer acetate and interferon beta for clinically isolated syndrome should be incorporated into a review of TA32. If this review is deferred it will mean that there will be a delay in recommendations for newer interferon beta treatments and treatments for clinically isolated syndrome.

8. Implementation

A submission from Implementation is included in Appendix 3.

Since 2002, following the publication of TA 32 and the introduction of the Risk Sharing Scheme there has been an increase in the volume of interferon beta-1a and glatiramer acetate prescribed and dispensed in hospitals in England. There has been a slight increase in the volume of interferon beta-1b prescribed and dispensed since TA 32 was issued, but remains lower than interferon beta-1a. Since the publication of TA 127 in 2007 there has been an increase in the volume of natalizumab dispensed or prescribed in hospitals in England.

9. Equality issues

There were no equalities issues raised in the appraisals of betainterferon and glatiramer acetate for the treatment of multiple sclerosis (TA 32); Natalizumab for the treatment of adults with highly active relapsing remitting multiple sclerosis (TA 127) or Fingolimod for the treatment of highly active relapsing- remitting multiple sclerosis.

GE paper sign off: Janet Robertson, 10 April 2013

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	**A review of the appraisal will be planned into the NICE's work programme.**	**Yes**
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Clinical Guideline CG8. Issued: November 2003. Update in progress. Publication expected in 2014.

Percutaneous venoplasty for chronic cerebrospinal venous insufficiency for multiple sclerosis. Interventional Procedures Guidance IPG420. Issued: March 2012.

In progress

Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. Technology Appraisal. Expected issue date: April 2014.

Laquinimod for the treatment of relapsing-remitting multiple sclerosis. Technology Appraisal. Expected issue date: February 2014.

Teriflunomide for the treatment of relapsing forms of multiple sclerosis. Technology Appraisal. Expected issue date: January 2014.

Dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis. Technology Appraisal. Expected issue date: January 2014.

Fingolimod for the treatment of primary-progressive multiple sclerosis. Technology Appraisal. Expected issue date: TBC. This appraisal has been on hold since 2011, pending updated regulatory timelines from the manufacturer.

Suspended/terminated

Interferon beta-1b, interferon beta-1a and glatiramer acetate for the treatment of single demyelinating event with clinically isolated syndrome. Technology Appraisal. This appraisal was originally referred to NICE in July 2009, with a specific remit that it would be carried out alongside any future review of TA32. As TA32 has been on the list of static guidance since the remit for clinically isolated syndrome was received this appraisal has effectively been suspended.

Cladribine for the treatment of relapsing-remitting multiple sclerosis. Technology Appraisal. Suspended in February 2011 – negative regulatory opinion.

Sativex as an add-on treatment of moderate to severe spasticity in multiple sclerosis. Technology Appraisal. Suspended in 2003 due to regulatory delays. Sativex is now licensed but has included in the scope for the update of clinical guideline on multiple sclerosis (CG8) and so work on the Technology Appraisal has been discontinued.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Interferon beta-1a (Avonex and Rebif-branded proprietary formulations) were considered according to their licensed indications, which covered only relapsing remitting MS. Interferon beta-1b (Betaferon-branded proprietary formulation) was considered according to its licensed indications, which included both relapsing remitting and secondary progressive MS.	No change. Note that an additional, proprietary formulation of interferon beta-1b (branded as Extavia) was approved by the EU in 2008, with a marketing authorisation which includes both relapsing remitting and secondary progressive MS. All the aforementioned interferon beta products are also licensed for use in people with a single demyelating event of a specified severity (clinically isolated syndrome). NICE has received a referral for these indications (see above).
Glatiramer acetate: the treatment of RRMS.	No change. Note that the marketing authorisation for glatiramer acetate limits its use to ambulatory patients only. Glatiramer acetate is also licensed for use in people with a single demyelating event of a specified severity (clinically isolated syndrome). NICE has received a referral for this indications (see above).

Indication considered in original appraisal	Proposed indication (for this appraisal)
Natalizumab: Single, disease-modifying therapy in highly active relapsing–remitting multiple sclerosis for: • Patients with rapidly evolving severe relapsing–remitting multiple sclerosis defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI. This patient group is referred to as the 'RES group'. • Patients with high disease activity despite treatment with interferon beta. This group is defined as patients who have failed to respond to a full and adequate course of a interferon beta. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion. This patient group is referred to as the 'suboptimal therapy group'.	As before The suboptimal therapy group could also be defined as including with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year, which would reflect the wording of the SPC.

Indication considered in original appraisal	Proposed indication (for this appraisal)
Fingolimod: Single, disease-modifying therapy in highly active relapsing–remitting multiple sclerosis for the following groups: • Adults with high disease activity despite treatment with a beta interferon. These patients may be defined as 'those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year'. • Adults with rapidly evolving severe relapsing–remitting multiple sclerosis defined by two or more disabling relapses in 1 year, and with one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	No change.

Details of new products and potential license extensions

Drug (manufacturer)	Details (phase of development, expected launch date,)
Multiple sclerosis vaccine (Opexa)	Phase II. UK launch plans unknown.
Alemtuzumab (Genzyme)	Pre-registration filings made. UK launch anticipated Q3 2013.
Arbaclofen placarbil (Xenoport)	Phase III. UK launch plans unknown.

Drug (manufacturer)	Details (phase of development, expected launch date,)
Daclizumab (Biogen Idec)	Phase III. UK launch planned Q4 2014.
Dimethyl fumarate (Biogen Idec)	Phase III. UK launch anticipated Q2 2013.
Fampridine (Biogen Idec)	Licensed in the UK for MS-related walking disability.
Fingolimod (Novartis)	Phase III trials for primary progressive MS are ongoing. Potential UK launch date for this extended license: Q4 2015.
Firategrast (GSK)	Phase II. UK launch plans unknown.
Goat serum antibodies (Aimspro)	Phase II. UK launch plans unknown.
Interferon beta-1b, recombinant human (Nuron)	Phase III. UK launch plans unknown.
Laquinimod (Teva)	Pre-registration filings made. UK launch anticipated Q3 2013.
Masitinib (AB Science)	Phase III. UK launch plans unknown.
Mitoxantrone (Immunex)	Licensed in the US. Used off-license in the UK. As it is no longer under patent there is no commercial interest in obtaining a licence for its use in MS in the UK (source: New Drugs Online)
Natalizumab (Biogen Idec)	Pre-registration filings made for a license extension to include first-line treatment of relapsing-remitting MS in people who have tested negative for antibodies to the JC virus. UK launch anticipated Q1 2014. Phase III for secondary progressive MS. UK launch plans unknow. Phase III trial scheduled to end December 2014.
Ocrelizumab (Roche)	Phase III for primary progressive and relapsing remitting MS. Filings not expected before 2015
ONO-4641 (Ono Pharmaceutical)	Phase II. UK launch plans unknown.
BIIB-017; Peginterferon beta-1a (Biogen Idec)	Pegylated form of interferon beta-1a. Phase III. UK launch anticipated Q4 2014
Ponesimod (Actelion)	Phase II. UK launch plans unknown.
Teriflunomide (Sanofi)	Pre-registration filings made. UK launch anticipated Q2 2013

Registered and unpublished trials

Trial name and registration number	Details
Natalizumab De-escalation With Interferon Beta-1b NCT01144052; EOC.NC.09.01.	Natalizumab vs. interferon beta in people who have previously taken natalizumab for at least 12 months. n=20 Estimated primary completion date: June 2012. Estimated completion date: June 2013.
RNF and Betaseron® Tolerability Study NCT00428584; 27133; REFORMS.	RCT of interferon beta-1a (rebif) (new formulation) vs. and interferon beta-1a, followed by 82 week follow-up in first arm. n=129 Completed
Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis (MS) CombiRx NCT00211887; GCO 02-0526; 02-0526; CRC; U01 NS45719.	Interferon beta-1a vs. glatiramer acetate vs. combination of the two. n=1008 Estimated completion date: July 2012
Fingolimod Versus Interferon Beta-1b in Cognitive Symptoms NCT01333501; CFTY720DIT01; 2010-023023-19.	n=150 Estimated completion date: June 2015
Patients With RRMS:Candidates for MS Therapy Change EPOC; NCT01317004; CFTY720DIT02; 2010-024017-31.	Fingolimod vs. interferon beta-1a or interferon beta-1b or glatiramer acetate in previously treated relapsing-remitting MS patients. n=264 Estimated completion date: December 2013
A Phase IV Study of Rebif ® 44mcg Administered Three Times Per Week by Subcutaneous Injection Compared With no Treatment in the Therapy of Relapsing Multiple Sclerosis After Mitoxantrone REMAIN; NCT00283140; IMP 25874.	n=30 Completed.

Trial name and registration number	Details
Stem Cell Therapy for Patients With Multiple Sclerosis Failing Interferon A Randomized Study NCT00273364; DI MS.Randomized2004.	Stem cell therapy vs. either interferon beta-1a; interferon beta-1b; glatiramer acetate; mitoxantrone; natalizumab; fingolimod. n=110 Estimated primary completion date: December 2013 Estimated completion date: December 2014
MOdification of VIsual Outcomes After Optic Neuritis in CIS or MS by Gilenya (MOVING Study) NCT01647880.	Fingolimod vs. interferon beta-1b in people with either clinically isolated syndrome or MS. n=88 Estimated completion date: April 2015
A 6-month, Randomized, Open-label, Patient OutComes, Safety and Tolerability Study of Fingolimod (FTY720) 0.5 mg/Day vs. Comparator in Patients With Relapsing Forms of Multiple Sclerosis NCT01216072; EPOC; CFTY720DUS01.	Fingolimod vs. interferon beta (various) or glatiramer acetate. n=1053 Completed
Phase 3 Study to Evaluate Efficacy and Safety of NU100 in Patients With Relapsing Remitting Multiple Sclerosis (RRMS) NCT01464905; CP-NU100-01.00.	NU 100 (unlicensed) vs interferon beta-1b vs. placebo. n=300 Estimated primary completion date: December 2013 Estimated completion date: December 2014
BRAVO Study: Laquinimod Double Blind Placebo Controlled Study in RRMS Patients With a Rater Blinded Reference Arm of Interferon β-1a (Avonex®) NCT00605215; MS-LAQ-302; EUDRACT 2007-005450-23.	n=1331 Completed.
Evaluation of Patient Retention of Fingolimod vs. Currently Approved Disease Modifying Therapy in Patients With Relapsing Remitting Multiple Sclerosis. PREFERMS; NCT01623596; CFTY720DUS09/	Study of treatment discontinuation with fingolimod; interferon beta and glatiramer acetate. n=1000 Estimated completion date: July 2015.

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Appendix 3 – Implementation feedback

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1 Routine healthcare activity data

1.1 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of Interferon beta 1A, Interferon beta 1B, glatiramer acetate and natalizumab prescribed and dispensed in hospitals by hospital pharmacies between July 2000 and January 2012 in England.

Figure 1 Volume of Interferon beta 1A and Interferon beta 1B prescribed and dispensed in hospitals in England

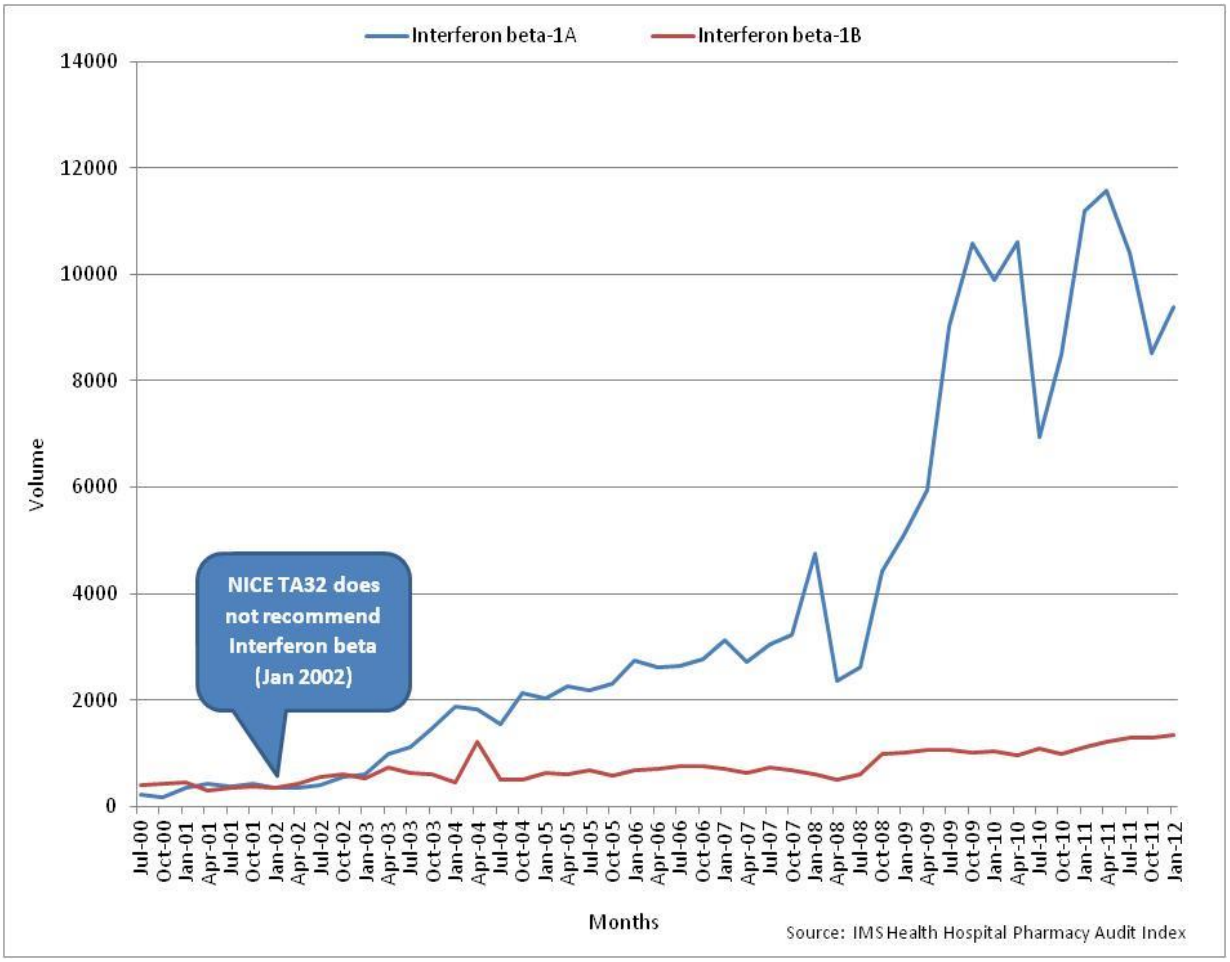


Figure 2 Cost of Interferon beta 1A and Interferon beta 1B prescribed and dispensed in hospitals in England

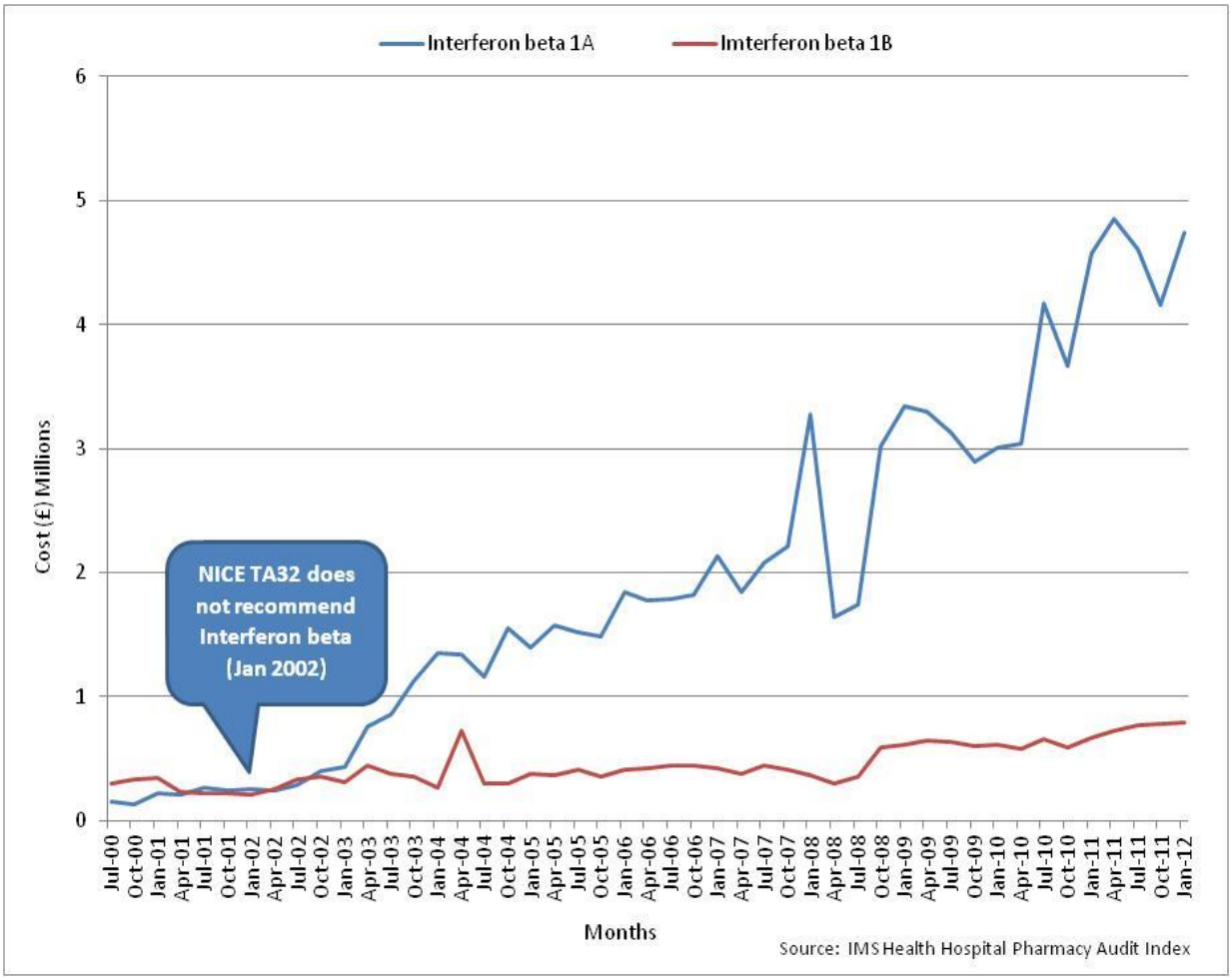


Figure 3 Cost and volume of Glatiramer acetate prescribed and dispensed in hospitals in England

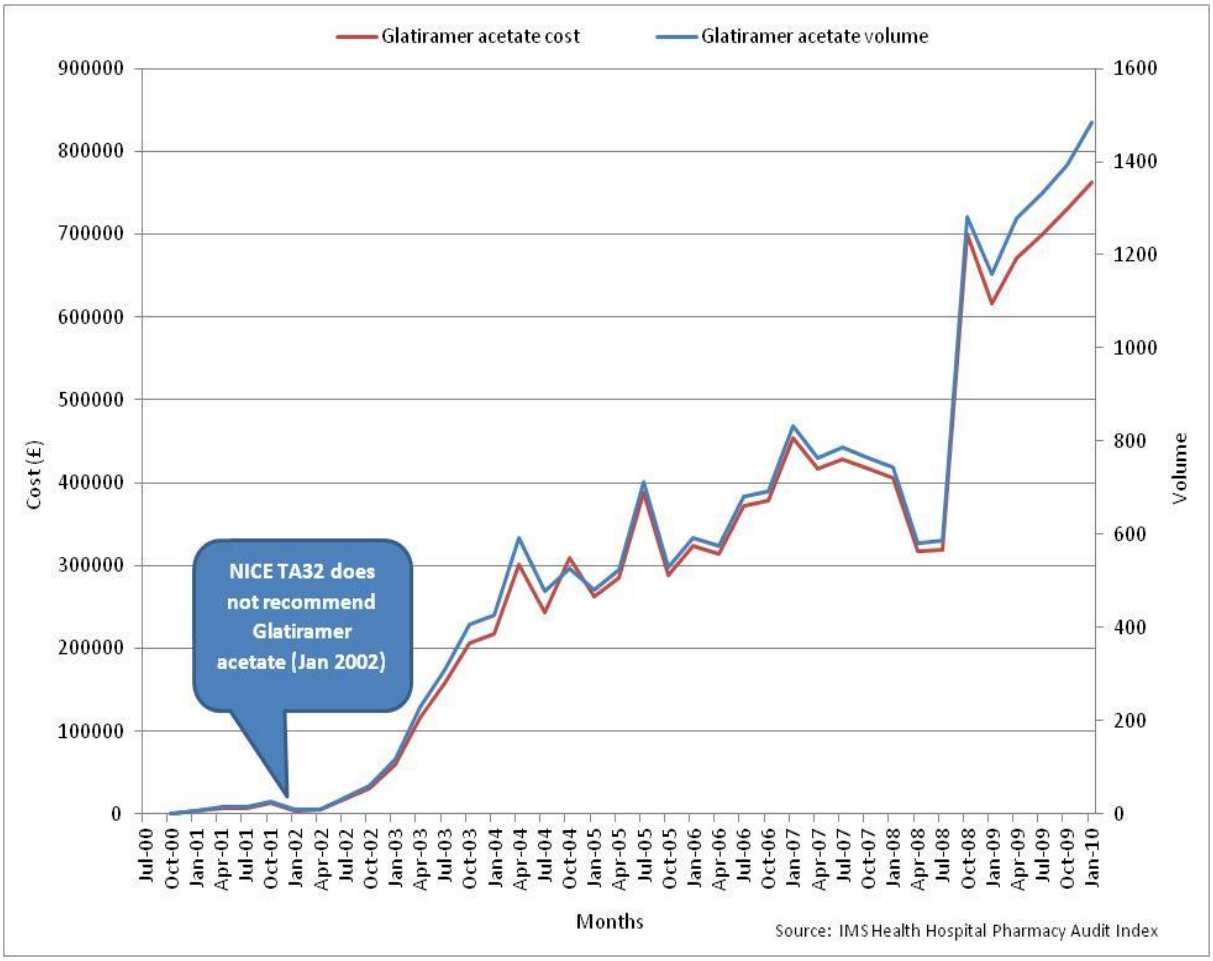
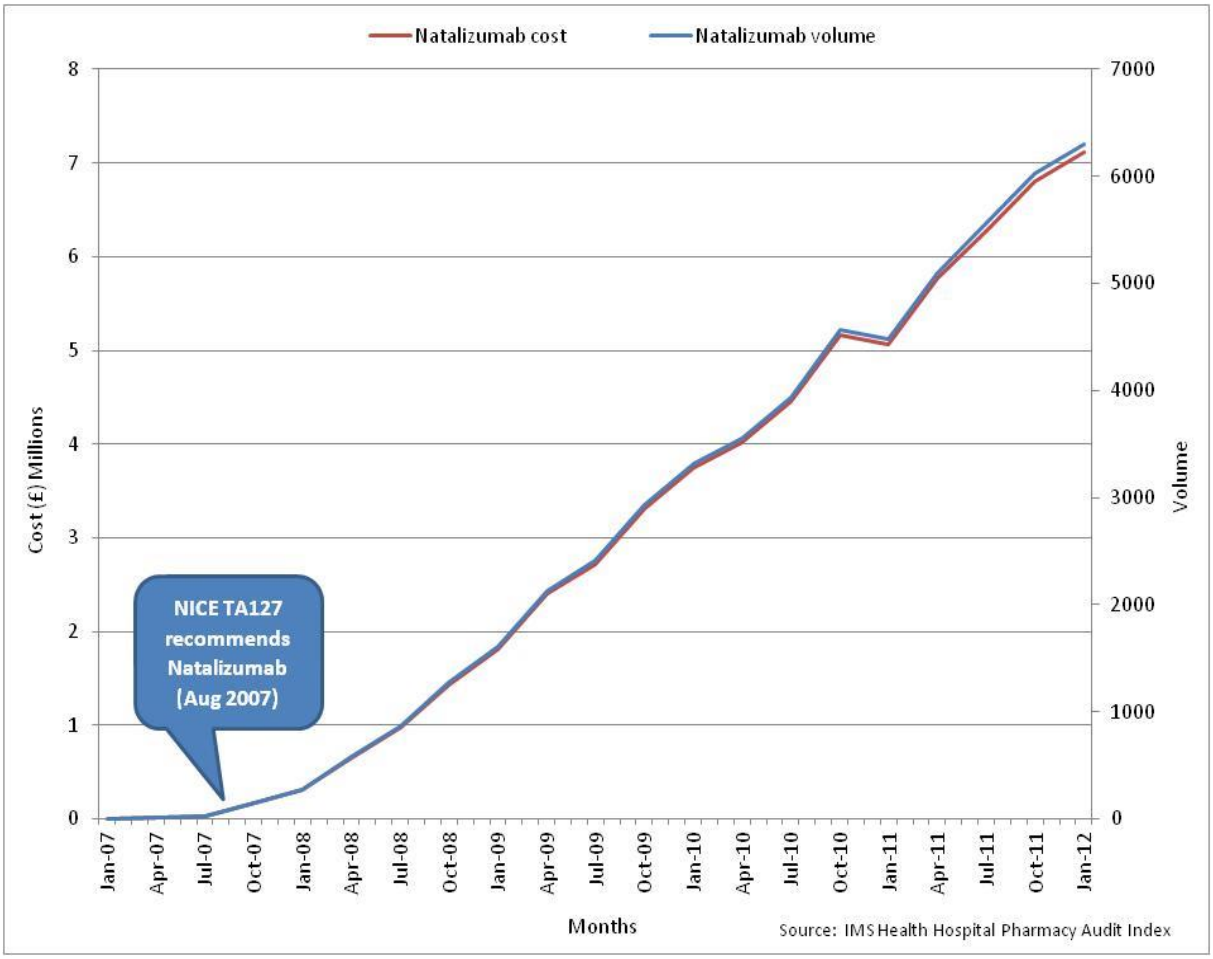


Figure 4 Cost and volume of Natalizumab prescribed and dispensed in hospitals in England



1.2 ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of Interferon Beta and Glatiramer acetate prescribed in primary care and in hospitals that has been dispensed in the community in England between November 2007 and October 2012.

Figure 5 Cost and volume of Interferon Beta prescribed in primary care and in hospitals, that has been dispensed in the community

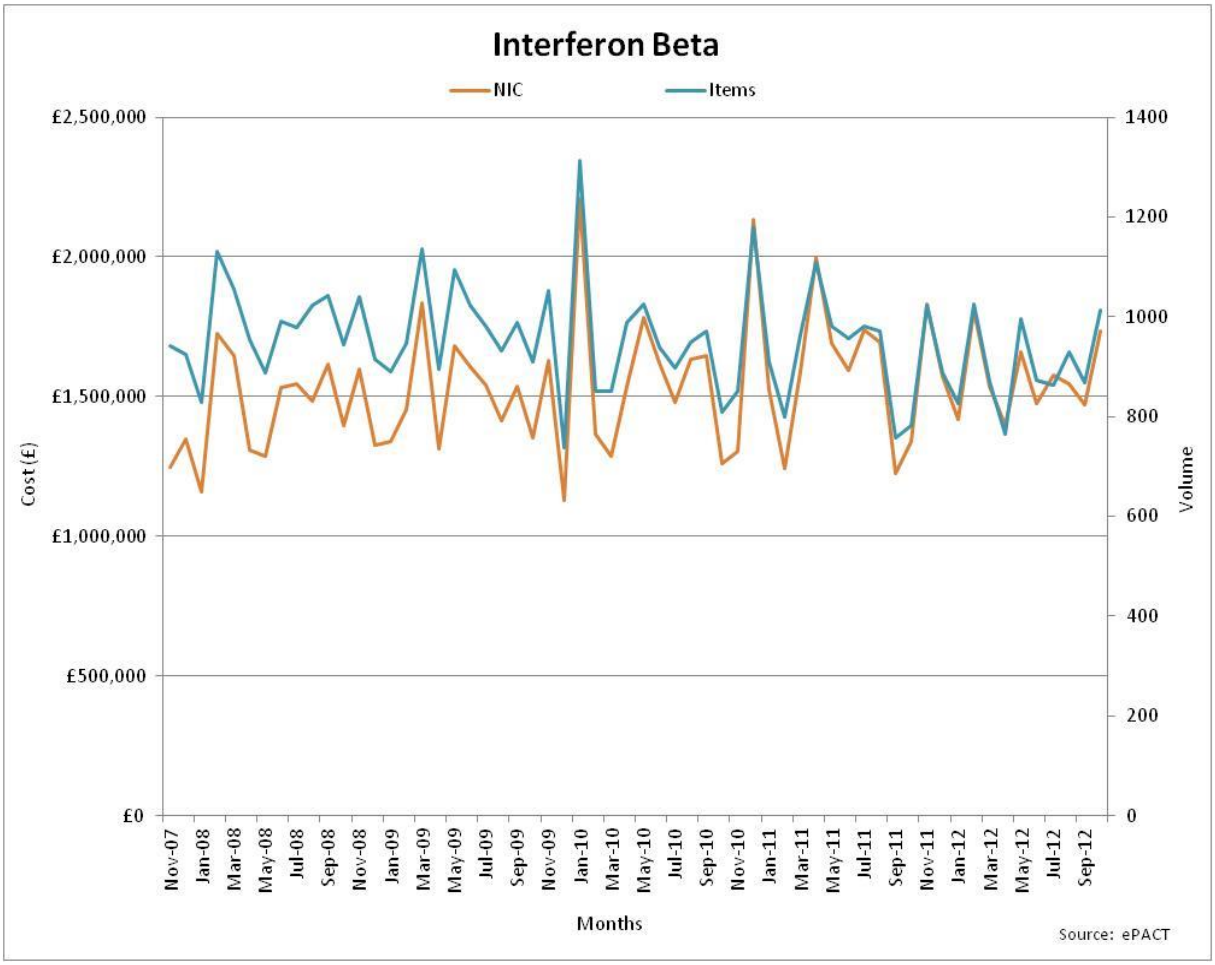
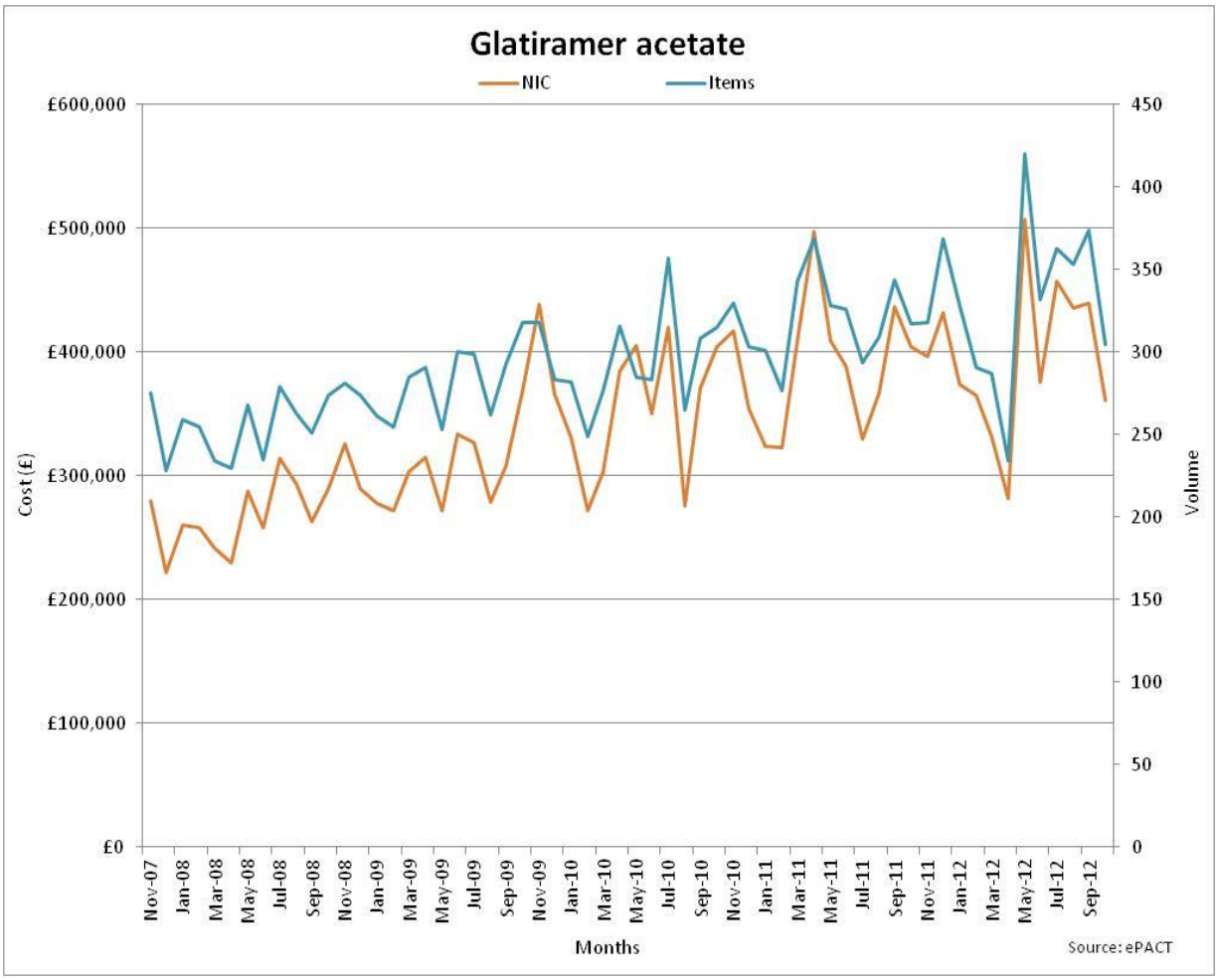


Figure 6 Cost and volume of Glatiramer acetate prescribed in primary care and in hospitals, that has been dispensed in the community



2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

The following article relates to the uptake of NICE TA127:

2.1 NHS Information Centre for Health and Social Care (2009) Use of NICE appraised medicines in the NHS in England-Experimental Statistics

The NICE costing template expected the annual equivalent of 419 patients giving a predicted use of 152.9 thousand doses per year. The observed use in 2008 was 91.0 thousand defined daily doses, a ratio of 0.6 to 1. Use was increasing over 2008 and

if the use in the first quarter of 2009 continued throughout the year then the use in 2009 would be 194.7 thousand DDDs which would give a ratio of 1.3 to 1.

The following article relates to the uptake of NICE TA127 and TA32:

2.2 Richards, M (2010) Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.

Appendix A: Healthcare activity data definitions

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions written in hospitals but dispensed in the community (FP10 [HP]) are not included in PACT data. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.