NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA221; Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura, and TA293; Eltrombopag for the treatment of chronic immune or idiopathic thrombocytopenic purpura

TA221 was issued in April 2011 and TA293 in July 2013.

The review date for both appraisals is March 2014.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

TA221: To appraise the clinical and cost effectiveness of romiplostim within its licensed indication for the treatment of refractory chronic idiopathic (immune) thrombocytopenic purpura**.**

TA293: To appraise the clinical and cost effectiveness of eltrombopag within its licensed indication for the treatment of refractory chronic idiopathic (immune) thrombocytopenic purpura.

3. Current guidance

TA221:

1.1. Romiplostim is recommended for the treatment of adults with chronic immune (idiopathic) thrombocytopenia purpura:

- whose condition is refractory to standard active treatments and rescue therapies or
- who have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

and

- if the manufacturer makes romiplostim available with the discount agreed as part of the patient access scheme.

1.2. Only a haematologist should start and supervise treatment with romiplostim.

TA293:

1.1 Eltrombopag is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if:

- their condition is refractory to standard active treatments and rescue therapies, **or**
- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

and

- the manufacturer provides eltrombopag with the discount agreed in the patient access scheme.

1.2 People currently receiving eltrombopag 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]

No new evidence has been identified that could be expected to lead to a change in the recommendations. Particularly, there are no data with which to directly compare the clinical effectiveness of romiplostim and eltrombopag. Therefore, it is proposed to place these appraisals on the static list.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from August 2007 (TA221) and March 2012 (TA293) 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

In Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (TA221), the Committee considered that the available evidence had

[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

limitations because it was derived from 2 small, placebo-controlled, randomised controlled trials (RCTs) and a non-comparative open-label study, and because the effectiveness of romiplostim compared with active treatment was unclear. The current literature search did not identify substantial new evidence for romiplostim. A new open-label study evaluated romiplostim for refractory immune thrombocytopenic purpura (ITP) (NCT00508820). However, this study was in patients who did not meet the inclusion criteria for other romiplostim trials, including those presented for TA221, so it could not be generalised to the population for which romiplostim was originally appraised.

No clinical trials compared eltrombopag with romiplostim directly in Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205) (TA293). Therefore, the Committee considered indirect evidence, but was concerned about the differences between the eltrombopag and romiplostim trials and the uncertainty associated with the estimates of the relative effectiveness of the 2 drugs with respect to platelet response. The current literature search did not identify any head-to-head trials between eltrombopag and romiplostim to address this uncertainty. However, a comparative utility study was identified (NCT01439321); it examined how the use of eltrombopag and romiplostim impacts the daily lives of chronic ITP patients, and so may be of limited value to an appraisal.

In TA293, the Committee was presented with interim results from EXTEND, an extension study that followed patients who had previously received eltrombopag in RCTs. The final results of this study are now published (Saleh et al. 2013). They showed no new or increased incidence of safety issues, and that long-term treatment with eltrombopag was generally well tolerated, and effective in maintaining platelet counts in the desired range. In addition, the current literature search identified an analysis of the impact of eltrombopag on bleeding in 5 clinical studies of adult chronic ITP previously considered by the Committee in TA293 (Tarantino et al. 2013). This analysis supported that eltrombopag significantly reduces bleeding in adult patients with chronic ITP compared with placebo.

The Committee recommended that research should be carried out to directly compare eltrombopag with non-thrombopoietin receptor agonist treatments routinely used in UK clinical practice. An RCT was designed to compare eltrombopag with intravenous immunoglobulin in ITP patients undergoing surgery (NCT01621204). However, no results appear to be available for this study.

In 2013, eltrombopag received a licence extension for the treatment of thrombocytopenia in adult patients with chronic hepatitis C virus infection, where the degree of thrombocytopenia is the main factor preventing the initiation of, or limiting the ability to maintain, optimal interferon-based therapy. However, this indication would not fall under the current remit. Eltrombopag and romiplostim have been investigated for the treatment of ITP in paediatric populations.

In summary, the evidence base for eltrombopag and romiplostim remains largely unchanged since TA293 and TA221 were published. A number of observational studies have been published recently, but these were generally small or single-centre. A Cochrane review of the efficacy and safety of eltrombopag and romiplostim for chronic ITP highlighted the lack of evidence on overall survival (Zeng et al. 2011). However, no new or ongoing RCTs formally studied this outcome. Furthermore, the

evidence base for eltrombopag and romiplostim is unlikely to change substantially in the near future because ITP is a rare and heterogeneous condition, which makes conducting comparative trials with these drugs difficult. The extension to the license of eltrombopag would not affect the recommendations in TA293, which relate to people who have ITP as their primary diagnosis. The list price of neither eltrombopag nor romiplostim has changed since NICE appraised these drugs. In view of the above information, an appraisal review of TA221 or TA293 is not needed.

Implications for Implementation

Although sections 1 in TA221 and TA293 are worded slightly differently, the recommendations for eltrombopag and romiplostim are intended for exactly the same patient population. The difference in wording stems from a change in the wording conventions in the time between the developments of these 2 technology appraisals, and could possibly lead to inconsistent interpretations of the two pieces of guidance. Consistent wording is necessary to support the development of pathways and entry to the BNF. Romiplostim and eltrombopag are commissioned through CCGs. In order to support consistent implementation of the 2 pieces of guidance across England, the wording of TA221 should be updated in line with current NICE wording conventions it is proposed to update the wording of the recommendations in TA221 in line with current NICE wording conventions and TA293, as follows:

TA221:

1.1 Romiplostim is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if:

- their condition is refractory to standard active treatments and rescue therapies, **or**

- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

and

- if the manufacturer makes romiplostim available with the discount agreed in the patient access scheme.

1.2 People currently receiving romiplostim 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.

8. Implementation

A submission from Implementation is included in Appendix 3.

Figure 1 shows that there has been a 5-fold increase in the cost and volume of romiplostim prescribed in England between April 2011, when TA221 was published, and the end of 2012. However, the extent to which TA221 drove this increase is unknown. The use of romiplostim in clinical practice was already increasing, albeit at a slower rate, when TA221 was published. Furthermore, in figure 2 for eltrombopag, which does not capture the impact of TA293, the amount of eltrombopag prescribed was increasing even though during that period eltrombopag was not recommended in the earlier TA205. This suggests that other factors may influence prescribing in clinical practice. So, while it is clear that TA221 has had some impact on romiplostim prescribing, further analyses are needed before this impact can be quantified.

Figure 2 does not show data after the publication of TA293, so the impact of TA293 on eltrombopag prescribing cannot be inferred from it.

9. Equality issues

In TA221, the Committee was aware that certain religious groups would not consent to the use of blood products, and also that ITP might affect pre-menopausal women more than men. It also understood that romiplostim might reduce the burden of hospital admission for long hours to receive intravenous immunoglobulin, especially for people for whom it is difficult to travel to a hospital. The Committee concluded that its recommendations do account for the individual needs of people to receive romiplostim, and do not make it more difficult for any particular group to access treatment with romiplostim compared with any other group.

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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.	No
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.	Yes

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

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
"Romiplostim has a marketing authorisation 'for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)'. The marketing authorisation also states that romiplostim 'may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated'."	Unchanged.
"Eltrombopag has a UK marketing authorisation for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in patients who have had a splenectomy and whose condition is refractory to other treatments (for example, corticosteroids or intravenous immunoglobulins), and as a second-line treatment for patients who have not had a splenectomy because surgery is contraindicated."	Unchanged for this specific indication. Eltrombopag is also licensed for "adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy."

Registered and unpublished trials

Trial name and registration number ***TA221 Romiplostim***	Details
An Open Label Study of Romiplostim in Adult Thrombocytopenic Subjects With Immune (Idiopathic) Thrombocytopenic Purpura (ITP). NCT00508820	Phase III interventional open label study. Completed. Enrolment: 407 (18 years and older). Primary completion date: March 2011 (no publication traced).

Trial name and registration number ***TA293 Eltrombopag***	**Details**
EXTEND (Eltrombopag Extended Dosing Study): An Extension Study of Eltrombopag Olamine (SB-497115-GR) in Adults, With Idiopathic Thrombocytopenic Purpura (ITP), Previously Enrolled in an Eltrombopag Study. NCT00351468 *The record has four papers attached. Three papers were previously captured for TA293, so have been considered already. The remaining paper was captured in this literature search (Tarantino et al, 2013) and it looks at bleeding using this study and four others.*	Phase III interventional open label study. Ongoing not recruiting. Estimated enrolment: 302 (18 years and older). Estimated primary completion date: July 2014.
Treatment of thromBocytopenia With EltRombopag or Intravenous Immune Globulin (IVIG) Before and DurING Invasive Procedures in Patients With Immune ThrombocytoPenia- BRIDGING ITP Study. NCT01621204	Phase III randomised trial. Not yet open for recruitment. Estimated enrolment: 74 (18 years and older). Estimated primary completion date: August 2015.
Study 200170: A Rollover Study to Provide Continued Treatment With Eltrombopag. NCT01957176	Phase IV. Open label study. Currently recruiting. Estimated enrolment: 100 (1 year and older). Estimated primary completion date: December 2023.
"End of EXTEND: Observing for Cure in Patients With Chronic ITP" NCT01386723	Phase not given. Prospective observational study. Currently recruiting. Estimated enrolment: 20 (18 years and older). Estimated primary completion date: June 2013.

Trial name and registration number ***Romiplostim and eltrombopag***	**Details**
Outcomes Comparison of Chronic Immune Thrombocytopenic Purpura (ITP) Patients Switched to Eltrombopag and Romiplostim. NCT01439321	Phase not given. Retrospective observational study. Study completed. Enrolment: 280 (18 years and older). Study completion date: June 2011 (no publication traced).
Long-term Safety Study of Treatment With the Thrombopoietin Agonists Eltrombopag and Romiplostim in Patients With Primary Immune Thrombocytopenia (ITP). NCT01443351	Phase not given. Prospective observational study. Currently recruiting. Estimated enrolment: 50 (18 years and older). Estimated primary completion date: March 2020.

References

Saleh MN, Bussel JB, Cheng G, Meyer O, Bailey CK, Arning M, et al. (2013) Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia (ITP): results of the long-term, open-label EXTEND study. *Blood.* 121: 537–545.

Tarantino MD, Fogarty P, Mayer B et al. (Apr. 2013) Efficacy of eltrombopag in management of bleeding symptoms associated with chronic immune thrombocytopenia. *Blood Coagulation & Fibrinolysis.* 24 (3): 284-296.

Zeng Y, Duan X, Xu J, Ni X. TPO receptor agonist for chronic idiopathic thrombocytopenic purpura. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD008235. DOI: 10.1002/14651858.CD008235.pub2.

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No. 221 and 293; Thrombocytopenic purpura - romiplostim and eltrombopag

Please contact Rebecca Braithwaite regarding any queries
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Contents

1. Routine healthcare activity data

1.1. ePACT data

Romiplostim and Eltrombopag are not prescribed in primary care or the community.

1.2. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost and volume of Romiplostim (figure 1) and Eltrombopag (figure 2) prescribed and dispensed for use in hospitals in England.

Figure 1 Cost and volume of Romiplostim prescribed and dispensed in hospitals in England

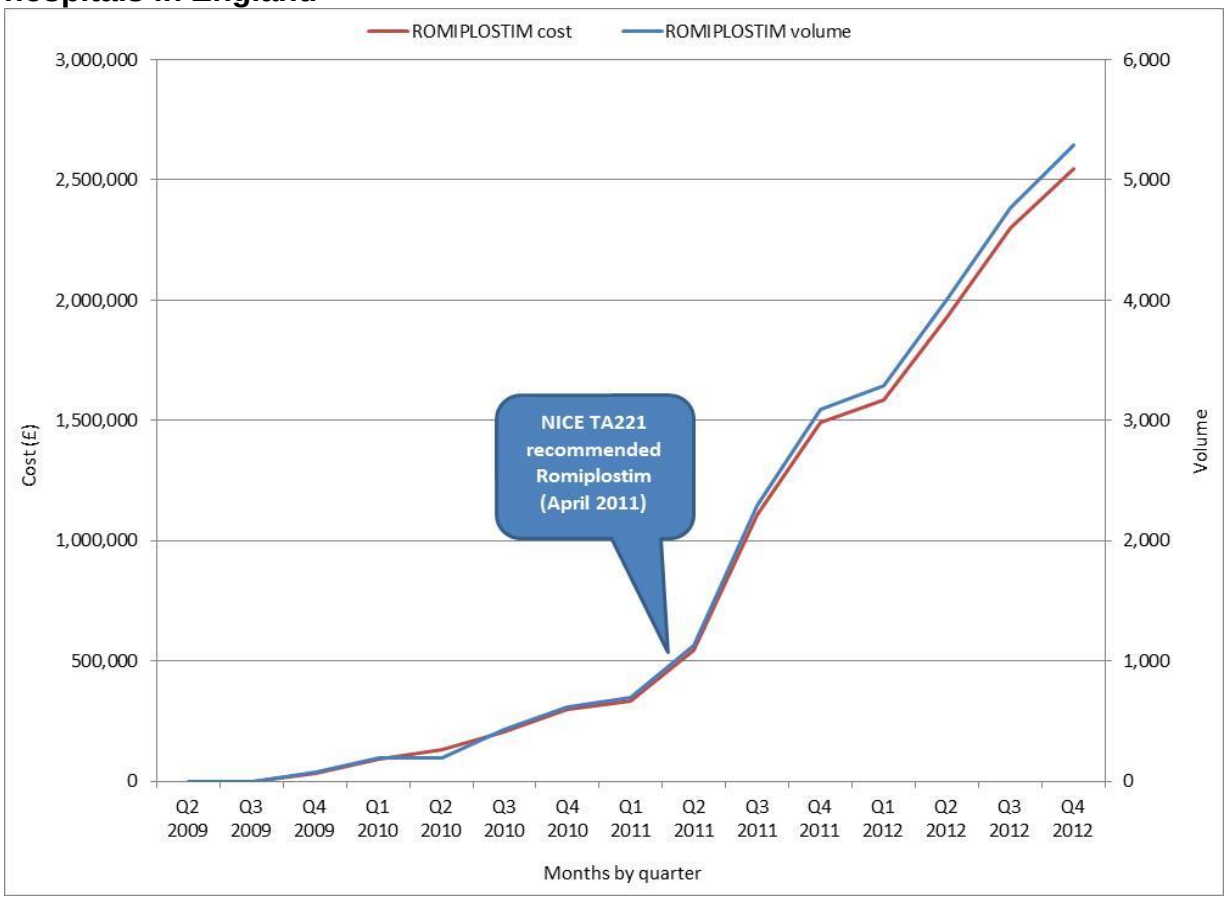
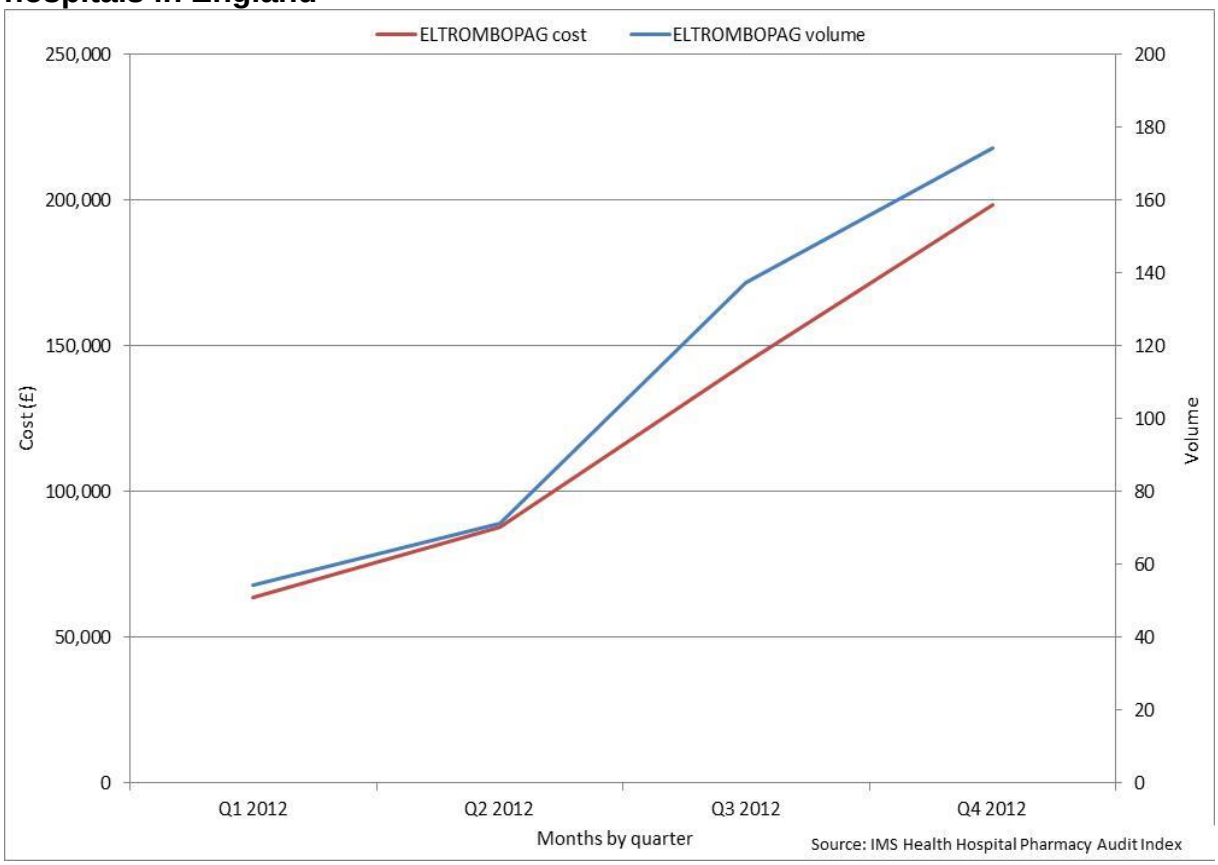


Figure 2 Cost and volume of Eltrombopag prescribed and dispensed in hospitals in England



2. Implementation studies from published literature

- Information is taken from the uptake database website.
- Nothing specific to add.

3. Qualitative input from the field team

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

Nothing specific to add.

Appendix A: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index

- 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.