# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# GUIDANCE EXECUTIVE (GE)

## Review of TA266; Mannitol dry powder for inhalation for treating cystic fibrosis, and TA276; Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis

TA266 was published in November 2012 and has a review date of October 2015.

TA276 was published in March 2013 and has a review date of December 2015.

The consideration of a review of these two appraisals has been expedited due to the clinical guideline for cystic fibrosis, which is currently in development.

### 1. Recommendation

The guidance should be incorporated into an on-going clinical guideline and the guidance moved to the static list. That we consult on this proposal.

### 2. Original remit(s)

TA266 - To appraise the clinical and cost effectiveness of mannitol dry powder for inhalation within its licensed indication for the treatment of cystic fibrosis

TA276 - To appraise the clinical and cost effectiveness of colistimethate sodium powder and tobramycin powder for inhalation within their licensed indications for the treatment of pseudomonas lung infection in cystic fibrosis.

### 3. Current guidance

**TA266:**

1.1. Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:

- who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and
- whose lung function is rapidly declining (forced expiratory volume in 1 second
- [FEV1] decline greater than 2% annually) and
- for whom other osmotic agents are not considered appropriate.

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

**TA276:**

1.1. Tobramycin dry powder for inhalation (DPI) is recommended as an option for treating chronic pulmonary infection caused by Pseudomonas aeruginosa in people with cystic fibrosis only if:

- nebulised tobramycin is considered an appropriate treatment, that is, when colistimethate sodium is contraindicated, is not tolerated or has not produced an adequate clinical response and
- the manufacturer provides tobramycin DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

1.2. Colistimethate sodium DPI is recommended as an option for treating chronic pulmonary infection caused by P. aeruginosa in people with cystic fibrosis only if:

- they would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered and
- the manufacturer provides colistimethate sodium DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

1.3. People currently using tobramycin DPI or colistimethate sodium DPI that is not recommended according to 1.1 or 1.2 should be able to continue treatment until they and their clinician consider it appropriate to stop. For children and young people this decision should be made jointly by the clinician, the child or young person and their parents or carers.

## 4. Rationale[1]

There is no new evidence that is likely to lead to a change in the recommendations in the original guidance (TA266 and TA276). It is therefore appropriate for the guidance to be incorporated into the ongoing clinical guideline (Cystic fibrosis: diagnosis and management of cystic fibrosis) and the guidance moved to the static list.

## 5. Implications for other guidance producing programmes

The Centre for Clinical Practice is currently developing a clinical guideline on cystic fibrosis. It is proposed that the guideline will incorporate the recommendations from TA266 and TA276, subject to completion of this review proposal.

[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

It is also planned for the guideline committee to review the evidence on the use of mannitol, colistimethate sodium and tobramycin dry powders in children and young people with cystic fibrosis not covered by the existing technology guidance, as part of the guideline.

## 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 March 2011 (TA266) and February 2011 (TA276) 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

The marketing authorisations for mannitol, tobramycin DPI and colistimethate sodium DPI are unchanged since the time of the original appraisal. Similarly, their prices are unchanged.

In relation to TA266, there is a lack of significant new clinical evidence further supporting the use of mannitol for treating cystic fibrosis in adults. Several publications describing further analyses from the clinical trials included in the original appraisal (CF-301 and CF-302) are available. In the original appraisal, the Committee concluded that the analyses carried out for the populations described as people using rhDNase and all people not using rhDNase reflected the population in the final marketing authorisation. Some evidence for the paediatric population is available, but this is not considered relevant because it is outside mannitol's licensed indication and therefore no recommendation for this population could be made in a NICE technology appraisal. In addition, it would be unlikely that a technology appraisal of mannitol for the paediatric population would add value to the NHS, given it is already commissioned for adults. It may therefore be appropriate for the Centre for Clinical Practice to consider including mannitol for the paediatric population in the cystic fibrosis guideline.

In relation to TA276, there are limited new data for tobramycin DPI and colistimethate sodium DPI. Some studies have investigated different treatment protocols, such as varying the frequency of administration. Further analyses of the EAGER trial (a key source of evidence in the original appraisal) have also been published. The phase III EDIT trial confirmed the efficacy of tobramycin inhalation powder produced using a modified manufacturing process (Galeva et al., 2012). However, no data were identified that would be likely to alter the Committee's conclusions in the original guidance.

In summary, there is no new evidence that is likely to lead to a change in the recommendations in the original guidance (TA266 and TA276).

## 8. Implementation

A submission from Implementation is included in Appendix 3. Because the 3 drugs are not used solely to treat cystic fibrosis (for example, they have more than 1 licensed indication), it is not possible to draw any conclusions from the implementation data.

## 9. Equality issues

In TA266 and TA276, the Committee concluded that its recommendations would not affect any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations.

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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. The review will be conducted through the [specify STA or MTA] process. | 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. The review will be conducted through the MTA process. | 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. The review will be conducted through the MTA process. | 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.<br>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal. | Yes |

| Options | Consequence | Selected – 'Yes/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.<br>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 |
| 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*

Respiratory tract infections – antibiotic prescribing: Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care (2008) NICE guideline CG69. Review decision: guidance has been placed on the static list (February 2014). Next review date: TBC

Cystic fibrosis: long-term azithromycin (2014) NICE advice ESUOM37

*In progress*

Cystic fibrosis: diagnosis and management of cystic fibrosis. NICE clinical guideline. Publication expected February 2017.

Clinical and cost effectiveness of lumacaftor in combination with ivacaftor within its marketing aurhorisation for treating cystic fibrosis in people who are homozygous for the F508del mutation. NICE technology appraisal. Currently consulting on draft scope

### Details of changes to the indications of the technology

| Indication and price considered in original appraisal | Proposed indication (for this appraisal) and current price |
|---|---|
| TA266<br>Mannitol dry powder is inhaled from a hand-held, breath-activated device. Mannitol has a marketing authorisation as an add-on therapy to best standard of care in adults with cystic fibrosis. The summary of product characteristics states that the recommended dose is 400 mg twice a day.<br><br>Mannitol is available as a 40 mg powder capsule for inhalation. The list price for a 14-day pack of 280 capsules and 2 inhalers is £231.66 (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] September 2012). This equates to £0.83 per 40 mg capsule, or an average cost of £16.55 per day, including the cost of the inhaler. These prices do not include VAT. Costs may vary in different settings because of negotiated procurement discounts. | Indication unchanged<br><br>Manufacturer has stated "As part of the EMA post marketing authorisation commitment, a cross-over study in patients aged 6-17 years old has been requested. This study is currently recruiting patients (https://clinicaltrials.gov/ct2/show/NCT01883531?term=mannitol+cystic+fibrosis&rank=9). The trial results are currently anticipated mid 2015 (subject to EMA discussions). It is not expected that over the next 12 months, a license will be granted that extends the current adult indication in CF.<br><br>Price of Mannitol is unchanged |
| TA276<br>Colistimethate sodium DPI is indicated for the management of chronic pulmonary infections caused by *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older.<br><br>The recommended dosage for colistimethate sodium DPI is 1 capsule (approximately equal to 125 mg of colistimethate sodium) to be inhaled twice daily using the 'Turbospin' inhaler device | Indication unchanged<br><br>Manufacturer has stated "There are no immediate plans to extend the indications for Colobreathe. A study in eradication in early Pseudomonas aeruginosa infection to be conducted as part of our paediatric investigation plan is unlikely to be completed until 2018 and hence any extension of the indications in cystic fibrosis are therefore |

| Indication and price considered in original appraisal | Proposed indication (for this appraisal) and current price |
|---|---|
| (PH&T Pharma) which is a breathactivated, reusable dry powder inhaler. The price for a 28-day pack including 1 Turbospin inhaler is £968 (excluding VAT; price provided by the manufacturer). The list price cost for 56 days of treatment is therefore £1936 excluding VAT. Costs may vary in different settings because of negotiated procurement discounts. | unlikely before the end of 2018".<br><br>Price of Colistimethate sodium DPI is unchanged |
| Tobramycin DPI is indicated for the suppressive treatment of chronic pulmonary infection caused by *P. aeruginosa* in adults and children aged 6 years and older with cystic fibrosis. | Indication unchanged |
| The recommended dosage for tobramycin DPI is 112 mg tobramycin (4×28-mg capsules), administered twice daily for 28 days using the Podhaler device in alternating cycles of 28 days on treatment followed by 28 days off treatment. The price for a pack of 56×28-mg capsules and 1 Podhaler device is £447.50 (excluding VAT; 'British national formulary' [BNF] edition 64). The list price cost for 56 days of treatment is therefore £1790 excluding VAT. Costs may vary in different settings because of negotiated procurement discounts. | Price of Tobramycin DPI is unchanged |

## Details of new products

| Drug (manufacturer) | Details (phase of development, expected launch date, ) |
|---|---|
| Tobramycin<br>*Vantobra*<br>(Pari Pharma) | Marketing authorisation granted 18 March.<br><br>Method of administration: Inhalation (nebulizer)<br><br>UK launch plans [redacted] |
| Amikacin liposomal<br>*Arikace*<br>(Insmed) | Phase 3 clinical trials<br><br>Method of administration: Inhalation (nebulizer)<br><br>UK launch plans [redacted] |
| Ataluren<br>*Translarna*<br>(Genzyme) | Phase 3 clinical trials<br><br>Method of administration: Oral<br><br>UK launch plans [redacted] |

| Drug (manufacturer) | Details (phase of development, expected launch date, ) |
|---|---|
| Ivacaftor<br>*Kalydeco*<br>(Vertex) | Method of administration: Oral<br><br>Launched in UK |
| Levofloxacin<br>Quinsair<br>(Adare Pharmaceuticals) | [redacted]<br><br>Method of administration: Inhalation (nebulizer)<br><br>UK launch plans [redacted] |
| Lumacaftor + Ivacaftor<br>(Vertex)<br><br>in homozygous F508del pts | Pre-registration (Filed)<br><br>Method of administration: Oral<br><br>UK launch plans [redacted] |

**Registered and unpublished trials**

| Trial name and registration number | Details |
|---|---|
| A Safety and Efficacy Trial of Inhaled Mannitol in Adult Cystic Fibrosis Subjects<br><br>NCT02134353<br><br>DPM-CF-303 | Phase 3 trial<br><br>Status: Recruiting<br><br>Estimated enrolment: 440<br><br>Estimated primary completion date: March 2016 |

**Relevant services covered by NHS England specialised commissioning**A01/P/a Clinical commissioning policy: Ivacaftor for Cystic Fibrosis NHS England

A01/PS/a Clinical commissioning policy statement: Inhaled Therapy for Adults and Children with Cystic Fibrosis NHS England

A01. Cystic fibrosis NHS England

"The NHS CB commissions the following drugs: dornase, tobramycin, colistimethate sodium, aztreonam lysine in line with the national CF Commissioning Policy" (November 2012) Manual for prescribed specialised services (covers Cystic fibrosis services for all ages).

Cystic Fibrosis NHS England Quality Dashboards

### Additional information

Colobreathe (colistimethate sodium dry powder for inhalation): risk of capsule breakage - new instructions for use Nov 2014 *(*Medicines and Healthcare products Regulatory Agency*)*

### References

Galeva I, Konstan MW, Higgins M et al. (2012) A challenging double-blind, placebo-controlled study of tobramycin inhalation powder in cystic fibrosis: Results of the EDIT trial. Journal of Cystic Fibrosis.Conference: 35th European Cystic Fibrosis Conference Dublin Ireland.Conference Start: 20120606 Conference End: 20120609.Conference Publication: (var.pagings).11 (pp S12), 2012.Date of Publication: June 2012.  (var.pagings): S12-.

# Appendix 3 – Implementation submission

## Routine healthcare activity data

Note that the prescribing data presented here needs to be treated with caution since these medicines have more than one licensed indication.

## 1.1 ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of drugs prescribed in hospitals and or the community and dispensed in the community in England.

**Figure 1 Cost and volume of tobramycin prescribed and dispensed in the community in England between April 2010 and September 2014.**

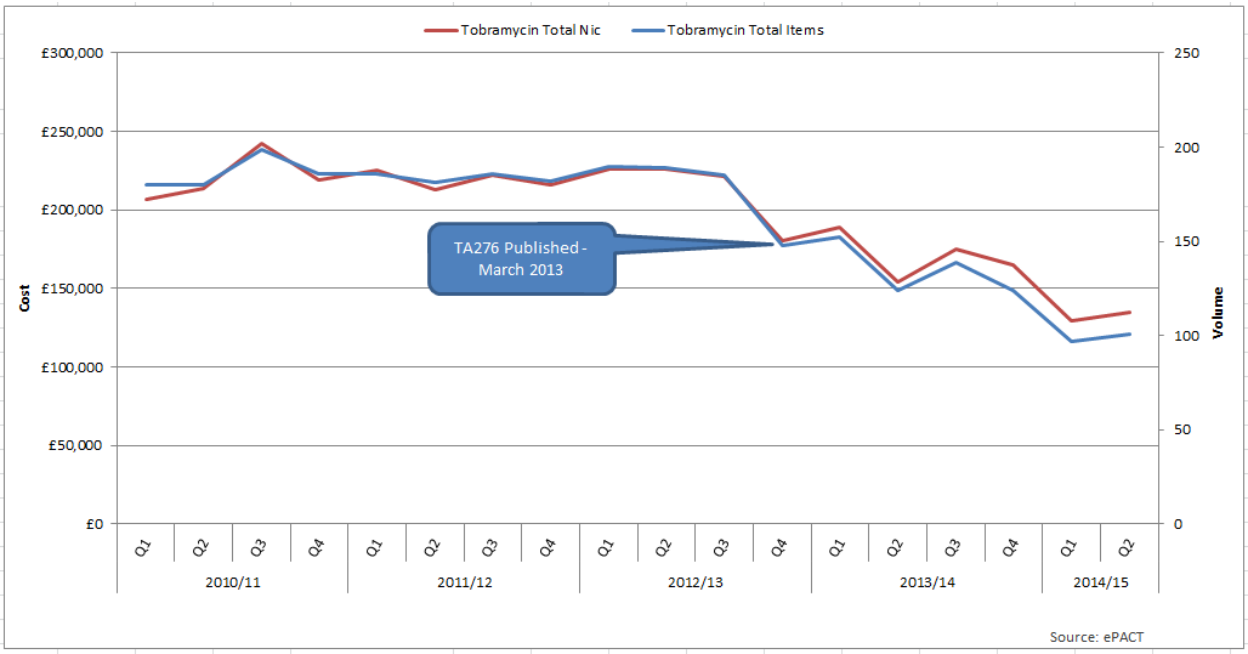



**Figure 2 Cost and volume of colistimethate sodium prescribed and dispensed in the community in England between April 2010 and September 2014.**

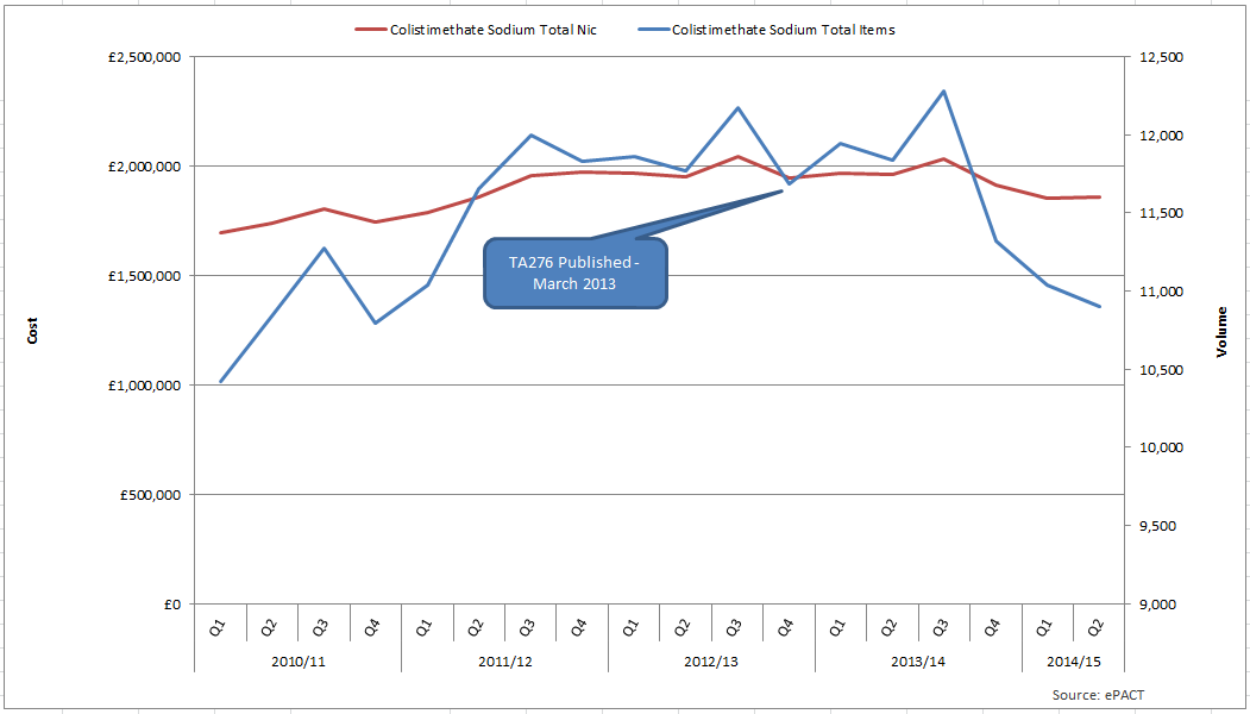



**Figure 3 Cost and volume of tobramycin prescribed in hospital and dispensed in the community in England between April 2010 and September 2014.**

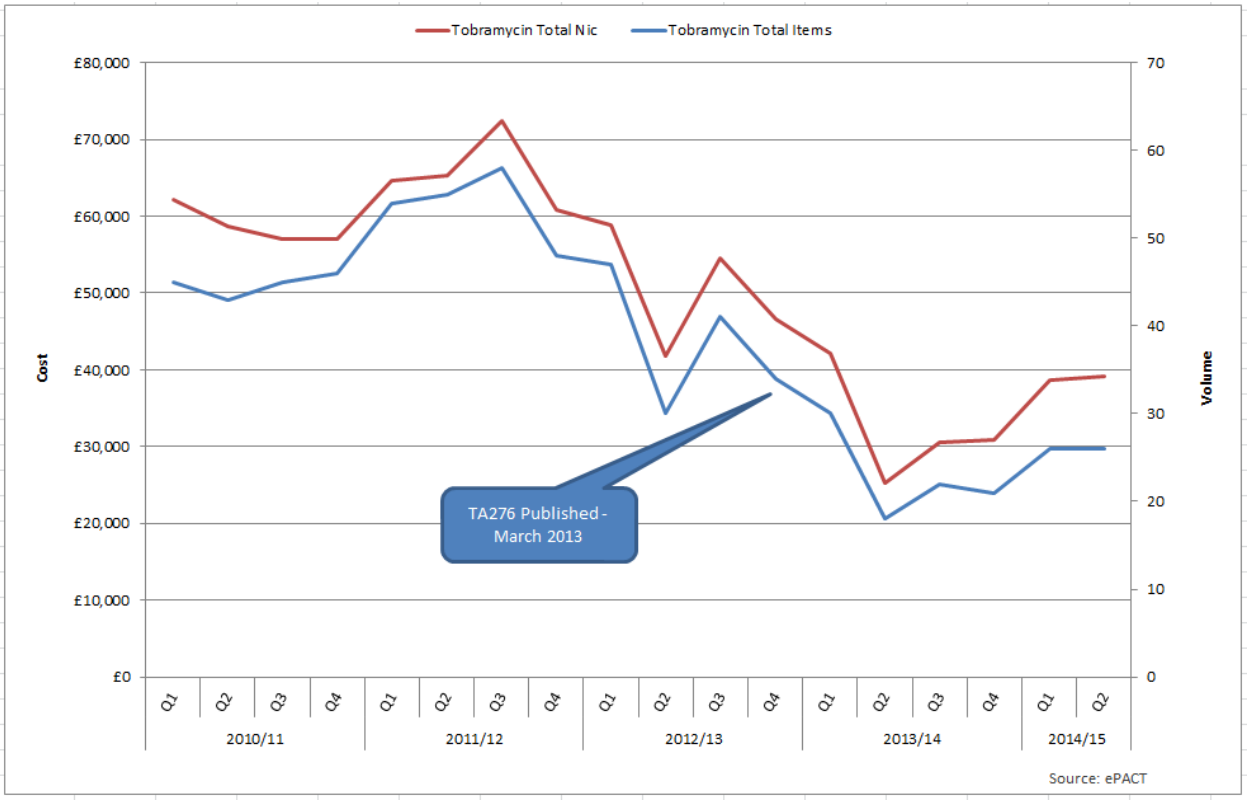
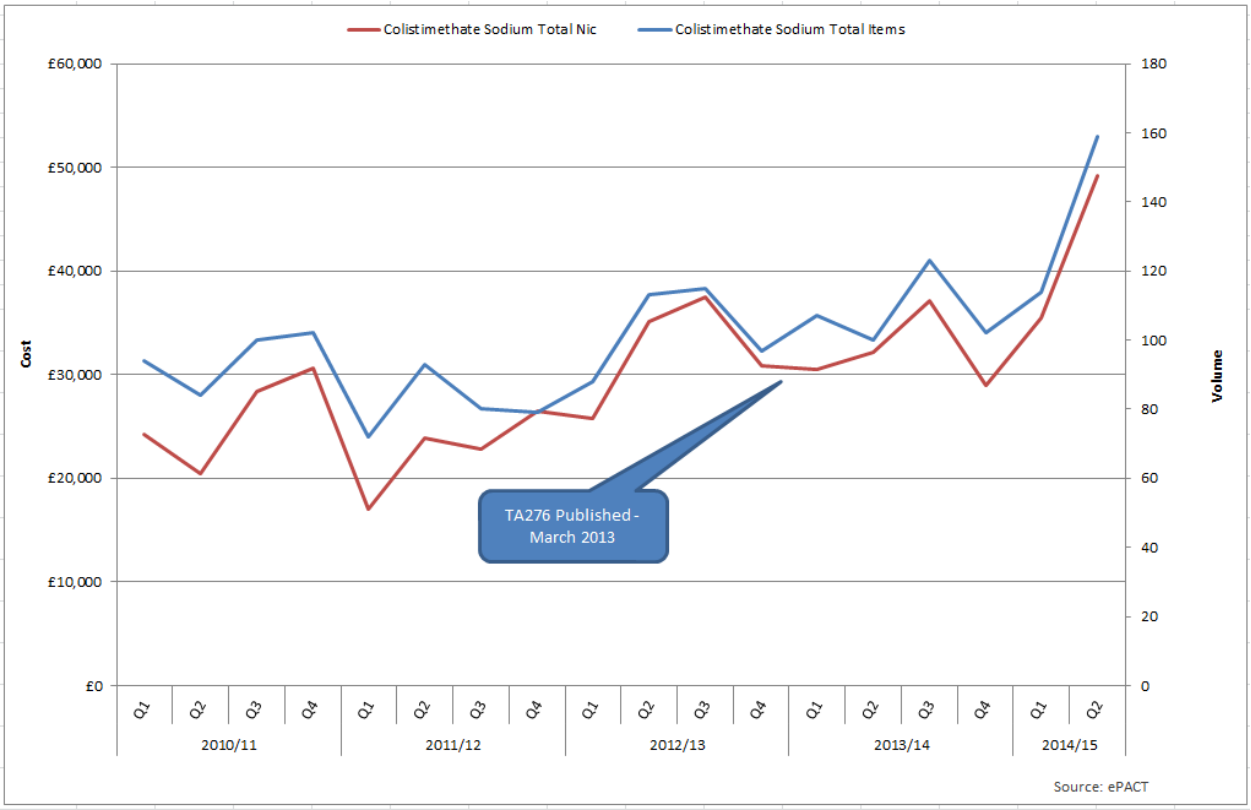


**Figure 4 Cost and volume of colistimethate sodium prescribed in hospital and dispensed in the community in England between April 2010 and September 2014.**




## 1.2 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of tobramycin and mannitol prescribed and dispensed in hospitals in England between January 2012 and December 2013. The volume relates to the number of packs used and should not be added together across various preparations due to differences in dosages/pack sizes.

**Figure 5 Cost and volume of tobramycin prescribed and dispensed in hospitals in England between January 2012 and December 2013.**

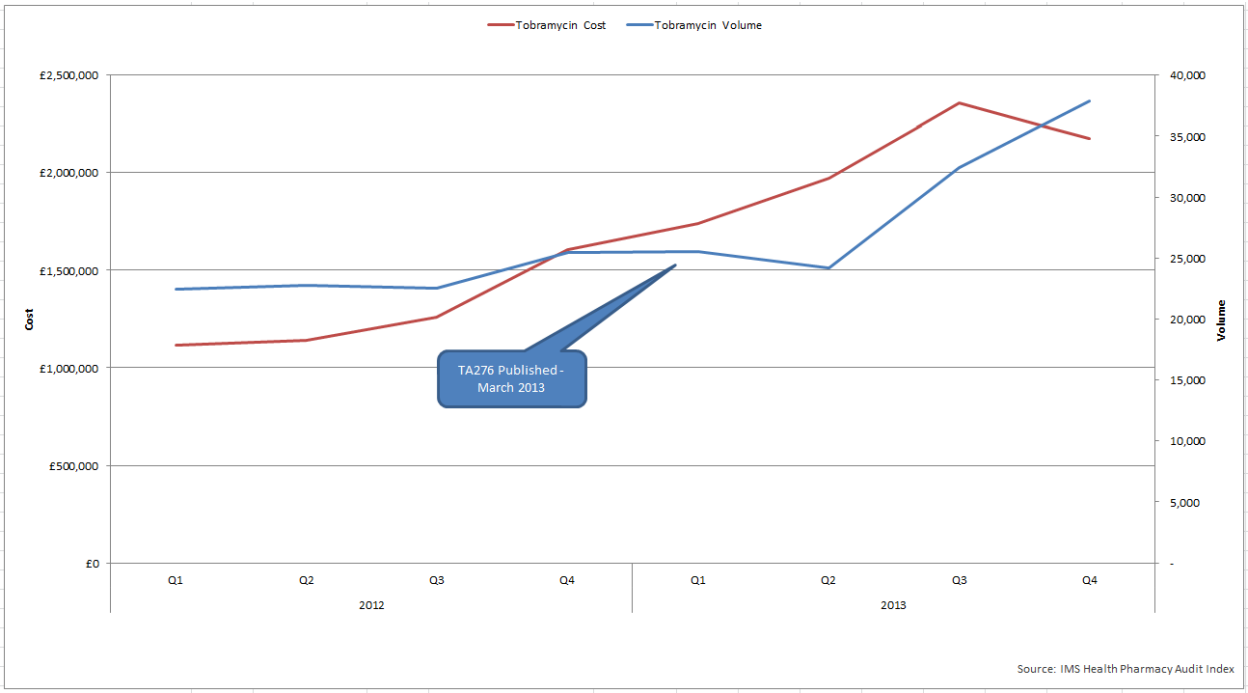
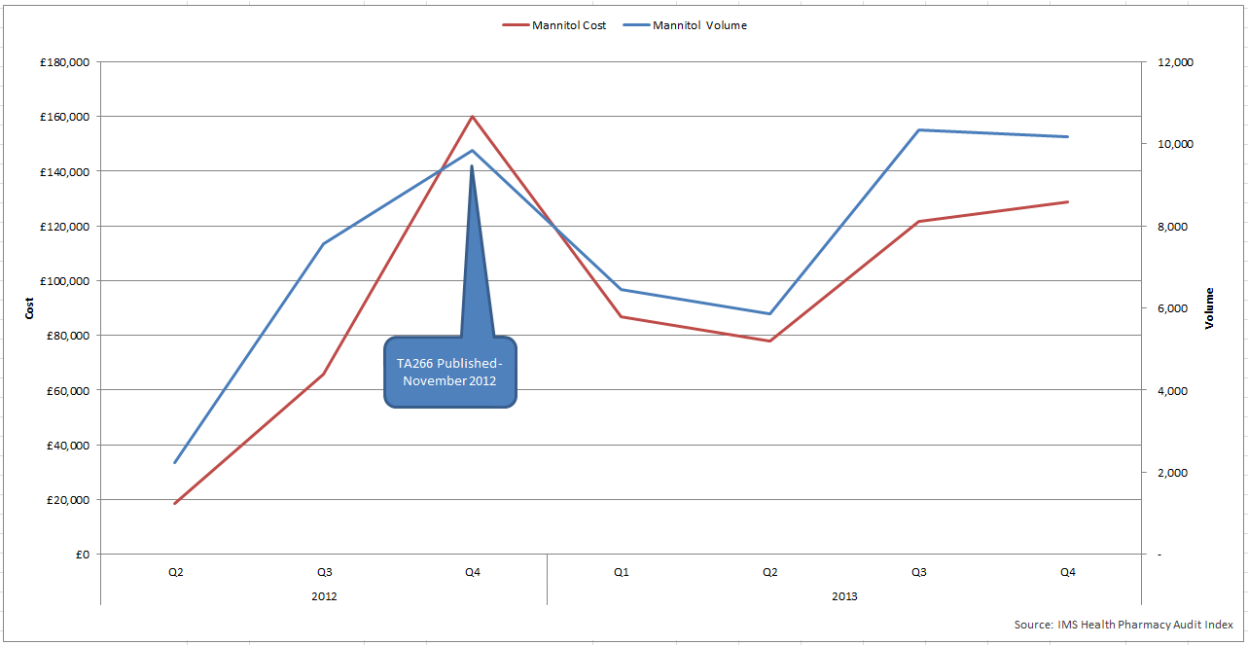



**Figure 6 Cost and volume of mannitol prescribed and dispensed in hospitals in England between January 2012 and December 2013.**




## 2. Implementation studies from published literature

No uptake information was found for TA266 or TA276.

## 3. Qualitative input from the field team

The implementation field team have not recorded any feedback in relation to this guidance.

## 4. Implementation studies from shared learning

A search of the shared learning website highlighted no examples of TA266 or TA276 being implemented.

## Supplementary information

*ePACT*

***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 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*

The hospital dispensing information is provided by IMS Health. It is based on information collected by IMS Health from the majority of hospitals in England. A minimum of 99% of acute English hospitals supply data to IMS Health about all medicines issued by hospital pharmacy departments. National figures are grossed up to give England level estimates on the basis of bed numbers. However sub-national figures are not adjusted in any way and will be an under estimate if trusts do not contribute data. Note that IMS Health revise figures as new data becomes available and so any figures may be different when extracted on a different occasion.

**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.