

Dornase alfa and mannitol for cystic fibrosis: analysis of utilisation

Drug utilisation sub-committee (DUSC)

October 2014

Abstract

Purpose

To examine the utilisation of dornase alfa and mannitol for cystic fibrosis (CF), including a predicted versus actual (PvA) analysis of mannitol in its first year of listing on the Pharmaceutical Benefits Scheme (PBS). At the February 2014 meeting, the DUSC requested an analysis of mannitol and dornase alfa to be considered at the same meeting as the 24 month PvA of tobramycin inhalation solution.

Date of listing on PBS

- Dornase alfa: 1 February 1996.
- Mannitol: 1 August 2012.

Data Source / methodology

Aggregate data from the DUSC Highly Specialised Drugs Database was used for data relating to packs, prescriptions and expenditure. The Department of Human Services Supplied Prescriptions Database was used for patient number and age.

Key Findings

In the 12 months from May 2013 to April 2014, 1,570 patients received dornase alfa and 106 patients received mannitol on the PBS. The utilisation of mannitol in its first year of listing was lower than expected. The utilisation of dornase alfa has increased steadily since 2004.

Purpose of analysis

To examine the utilisation of dornase alfa and mannitol for cystic fibrosis (CF), including a predicted versus actual (PvA) analysis of mannitol in its first year of listing on the Pharmaceutical Benefits Scheme (PBS). At the February 2014 meeting, the DUSC requested an analysis of mannitol and dornase alfa to be considered at the same meeting as the 24 month PvA of tobramycin inhalation solution.

Background

Pharmacology

Dornase alfa is a recombinant deoxyribonuclease I (DNase), an enzyme which cleaves extracellular DNA, reducing the viscosity of sputum in patients with CF.¹ The defined daily dose of dornase alfa is 2.5 mg (inhaled).

Mannitol is believed to change the viscoelastic properties of mucus, increase the hydration of the periciliary fluid layer and contribute to increased mucociliary and cough clearance of the retained secretions.² The defined daily dose of mannitol is 0.8 g inhaled.

Therapeutic Goods Administration (TGA) approved indications

Dornase alfa is indicated for the management of demonstrated respiratory complications in CF. Continued use should depend on demonstrating a sustained benefit.¹

Mannitol is indicated for the treatment of CF in both paediatric and adult populations six years and above as either an add-on therapy to dornase alfa or in patients intolerant to, or inadequately responsive to dornase alfa. Mannitol can trigger bronchoconstriction in patients with hyperresponsive airways. The initial dose of mannitol must be administered under clinical supervision according to the protocol outlined in the Product Information. The protocol requires measurement of oxygen saturation, spirometry and facilities to manage acute bronchospasm and availability of resuscitation equipment.²

Dosage and administration

Dornase alfa is administered at a dose of 2.5 mg (one ampoule) once daily through a nebuliser. Patients over the age of 21 may benefit from twice daily dosing. Dornase alfa can be used in infants.¹

Mannitol is administered at a dose of 400 mg (10 capsules) twice daily using the inhalation device.²

¹ Pulmozyme® (dornase alfa) Australian approved Product Information. Sydney: Roche Products Pty Ltd. Approved 29 November 1994, updated 6 May 2014. Available from <www.ebs.tga.gov.au>. Accessed 9 July 2014.

² Bronchitol® (mannitol) Australian approved Product Information. Sydney: Pharmaxis Ltd. Approved 7 February 2011, updated 10 January 2014. Available from <www.ebs.tga.gov.au>. Accessed 10 July 2014.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

PBS listing details (as at 1 August 2014)

Mannitol and dornase alfa have Section 100 Highly Specialised Drugs (HSD) Program listings.

Table 1: PBS listing of mannitol and dornase alfa

Item	Name, form & strength, pack size	Max. quant.	Repeats	DPMQ*	Brand name and manufacturer
2015C (Public)	MANNITOL Mannitol pack containing 280 capsules containing powder for inhalation 40 mg and 2 inhalers, 1	4	5	\$1736.00	Bronchitol® Pharmaxis Ltd
2008Q (Private)	MANNITOL Mannitol pack containing 280 capsules containing powder for inhalation 40 mg and 2 inhalers, 1	4	5	\$1782.76	Bronchitol® Pharmaxis Ltd
5704F (Public)	DORNASE ALFA dornase alfa 2.5 mg/2.5 mL inhalation: solution, 30 x 2.5 mL ampoules	2	5	\$2360.00	Pulmozyme® Roche Products Pty Ltd
6120D (Private)	DORNASE ALFA dornase alfa 2.5 mg/2.5 mL inhalation: solution, 30 x 2.5 mL ampoules	2	5	\$2406.76	Pulmozyme® Roche Products Pty Ltd

Source: August 2014 PBS Schedule, *Published price. A Special Pricing Arrangement applies to mannitol.

Restriction (abridged)

Mannitol and dornase alfa have PBS listing for use in CF. Both have Authority Required (Streamlined) listings for public hospitals and Authority Required listings for private hospitals.

Mannitol

- Cystic fibrosis patients 6 years of age or older intolerant or inadequately responsive to dornase alfa; and
- the patient has a negative hyperresponsiveness test as per the TGA approved Product Information; and
- forced expiratory volume in 1 second (FEV1) greater than 30 % predicted for age, gender and height; and
- evidence of chronic suppurative lung disease

To be eligible for continuing treatment following initial 3 months treatment the following criteria need to be met:

- no deterioration in FEV1 compared to baseline; and
- patient or the patient's family (in the case of paediatric patients) must report improvement in the patient's airway clearance; and
- the treating physician(s) must report a benefit in the clinical status of the patient.

Patients may continue treatment where treatment is providing a worthwhile benefit. There is also a 'grandfather' restriction for patients who started mannitol treatment prior to PBS listing.

Dornase alfa

For patients 5 years of age or older:

- Cystic fibrosis patients 5 years of age or older with evidence of chronic suppurative lung disease; and
- forced vital capacity (FVC) greater than 40 % predicted for age, gender and weight.

Patients under 5 years of age:

- Cystic fibrosis with a severe clinical course with frequent respiratory exacerbations or chronic respiratory symptoms (including chronic or recurrent cough, wheeze or tachypnoea) requiring hospital admissions more frequently than 3 times per year; OR
- Patient must have significant bronchiectasis on chest high resolution computed tomography scan; OR
- Patient must have severe cystic fibrosis bronchiolitis with persistent wheeze non-responsive to conventional medicines; OR
- Patient must have severe physiological deficit measure by forced oscillation technique or multiple breath nitrogen washout and failure to respond to conventional therapy.
- Following an initial 6 months' therapy, a comprehensive assessment must be undertaken and documented involving the patient, the patient's family, the treating physician and an additional independent member of the cystic fibrosis treatment team to establish agreement that dornase alfa treatment is continuing to produce worthwhile benefit.
- Patients who started treatment prior to 5 years of age may continue treatment where treatment is providing a worthwhile benefit.
- Patients under 5 years of age who started treatment prior to 1 November 2009 have a 'grandfather' restriction and may continue treatment where treatment is providing a worthwhile benefit.

Patients cannot receive both PBS-subsidised mannitol and dornase alfa. Refer to the [PBS website](#) for the complete restrictions for mannitol and dornase alfa.

Date of listing on PBS

Dornase alfa was listed on 1 February 1996 and was restricted to patients over 5 years of age. Listing was extended to patients under 5 years of age meeting certain criteria in November 2009.

Mannitol was listed on the PBS on 1 August 2012.

Current PBS listing details are available from the [PBS website](#).

Relevant aspects of the PBAC consideration

Dornase alfa was recommended for PBS listing by the PBAC at its September 1995 meeting. At its July 2009 meeting, the PBAC recommended extending the listing of dornase alfa to include the treatment of cystic fibrosis in children less than five years of age meeting certain clinical criteria. This recommendation was made following a number of submissions from the sponsor and advice from clinician groups to identify the group of patients aged 5 years or under who would benefit from treatment.

Mannitol was recommended for PBS listing at the March 2012 PBAC meeting.

Its first consideration by PBAC was at the March 2011 PBAC meeting. The submission presented an option of two listings. Both options were broadly for patients with an inadequate response to dornase alfa, intolerant to dornase alfa or who had not met continuing PBS criteria for dornase alfa. Both requested listings allowed for use as add-on therapy in patients who had an inadequate response to dornase alfa. The submission was rejected due to an inappropriate comparator where dornase alfa has failed; and uncertain clinical and cost-effectiveness when used in combination with dornase alfa.

For further details refer to the [Public Summary Document](#) from the March 2011 PBAC meeting.

Mannitol was considered for a second time at the November 2011 PBAC meeting. The PBAC rejected the submission because the comparator was inappropriate, and on the basis of uncertain clinical effectiveness and uncertain cost effectiveness.

For further details refer to the [Public Summary Document](#) from the November 2011 PBAC meeting.

At its March 2012 meeting the PBAC recommended the listing of mannitol on a cost-minimisation basis to a mixed comparator of 70 % dornase alfa and 30 % hypertonic saline. The PBAC considered that, due to the nature of cystic fibrosis and the cycling of treatments, it was likely that the majority of mannitol use would be as monotherapy rather than add-on therapy. The PBAC noted the sponsor's offer to provide mannitol to patients receiving combination therapy via a compassionate use scheme. The PBAC stated that there should be no additional cost to the Government budget with the listing of mannitol on the PBS.

A public summary document is not available for this consideration, as it was a minor submission.

Approach taken to estimate utilisation

Recent predictions of utilisation are not available for dornase alfa.

Mannitol

The submission used a mixed epidemiological and market share approach to estimate utilisation of mannitol. The data sources used to derive the eligible population are presented in Table 2.

Table 2: Sources used to estimate eligible population

Data	Value	Source
Total number of cystic fibrosis patients in Australia	-	11 th annual report from the Australian Cystic Fibrosis Registry (1998-2008). Forecast based on 3.3% annual increase in CF population. This is the average increase in prevalence from 2004 to 2008.
Proportion \geq 6 years of age	17.4%	Australian Cystic Fibrosis Registry (1998-2008).
FEV1<40%	7.6%	Australian Cystic Fibrosis Registry (1998-2008).
Patients not being treated due lack of respiratory symptoms (healthy)	21.5%	Australian Cystic Fibrosis Registry (1998-2008). The registry figure is 35.9%. The sponsor stated it is 60% of this figure (i.e. 21.5%).
Proportion failing dornase due to allergy	3%	Proportion of patients intolerant to dornase alfa is based on the discontinuation rate reported in the Fuchs et al (1994) trial.
Proportion failing dornase due to continuation criteria	33%	<i>The proportion of patients unresponsive to dornase alfa is based on an unknown source</i>
Proportion of patients who respond but stop therapy	36%	Sponsor-commissioned BIOGRID study, which was a retrospective observational study of cystic fibrosis patients managed through three Australian hospitals (Royal Children's Hospital, Monash Medical Centre and The Alfred Hospital, all located in Melbourne) between 1993 and 2010.
Proportion of patients who respond and continue therapy	64.0%	Sponsor-commissioned BIOGRID study, which was a retrospective observational study of cystic fibrosis patients managed through three Australian hospitals (Royal Children's Hospital, Monash Medical Centre and The Alfred Hospital, all located in Melbourne) between 1993 and 2010.
Proportion of patients who will re-trial dornase alfa	80%	Assumption.
Treatment trial rates for DPI mannitol monotherapy	50%	Pharmaxis marketing data. Applied to all groups of patients

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Proportion \geq 6 years of age	17.4%	Australian Cystic Fibrosis Registry (1998-2008).
FEV1<40%	7.6%	Australian Cystic Fibrosis Registry (1998-2008).
Patients not being treated due lack of respiratory symptoms (healthy)	21.5%	Australian Cystic Fibrosis Registry (1998-2008). The registry figure is 35.9%. The sponsor stated it is 60% of this figure (i.e. 21.5%).
Proportion failing dornase due to allergy	3%	Proportion of patients intolerant to dornase alfa is based on the discontinuation rate reported in the Fuchs et al (1994) trial.
Proportion failing dornase due to continuation criteria	33%	<i>The proportion of patients unresponsive to dornase alfa is based on an unknown source</i>
Response rate for DPI mannitol monotherapy	50%	Assumption. Purposeful overestimation of response rate reported in clinical trials.
Compliance to DPI mannitol and dornase alfa	100%	Assumption.
DPI mannitol PBS price	\$REDACTED	Weighted price based on the expected substitution of dornase alfa and hypertonic saline. The submission assumes that 70% of the DPI mannitol market would come from dornase alfa with the remaining 30% coming from hypertonic saline
DPI mannitol patient co-payments	-	Assumption. No patient co-payments

Source: November 2011 Commentary, p74. March 2012 Secretariat Overview

An overview of the derivation of estimates is presented in Figure 1.

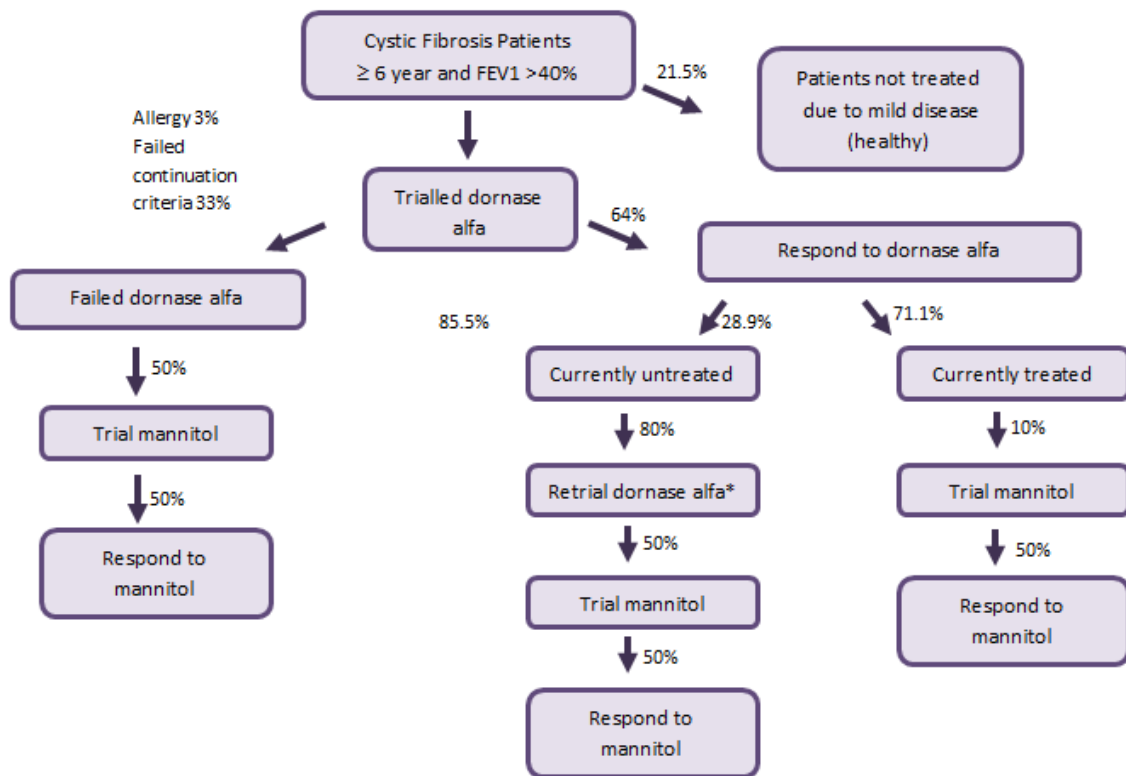


Figure 1: Derivation of mannitol estimates

Source: November 2011 Commentary, Final Estimates Model

*The estimates were calculated that only the patients who retrial dornase would trial mannitol

An overview of final estimates is presented in Table 3.

Table 3: Overview of mannitol estimates (effective prices)

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients who have trialled dornase alfa	1,940	2,010	2,081	2,155	2,232
Patients who have failed dornase	175	181	187	194	201
Patients using dornase	44	46	47	49	51
Patients previously using dornase	90	93	96	100	103
Total patients	309	320	331	343	355
Total packs (26 packs/patient/year)	8,051	8,338	8,635	8,943	9,262
Gross cost to PBS	\$REDACTED	\$REDACTED	\$REDACTED	\$REDACTED	\$REDACTED
Co-payments	\$REDACTED	\$REDACTED	\$REDACTED	\$REDACTED	\$REDACTED
Net cost to PBS	\$REDACTED	\$REDACTED	\$REDACTED	\$REDACTED	\$REDACTED

Reduced cost of other drugs	Year 1	Year 2	Year 3	Year 4	Year 5
Patients switching from dornase	244	253	262	271	281
Cost offset due to reduced dornase use (\$9,196/patient /year)	\$2,244,172	\$2,324,211	\$2,407,104	\$2,492,954	\$2,581,865
Net cost to PBS	\$REDACTED	\$REDACTED	\$REDACTED	\$REDACTED	\$REDACTED

Source: Mannitol final estimates

Previous reviews by the DUSC

The DUSC examined the utilisation of tobramycin solution for inhalation in its first year of listing for *Pseudomonas aeruginosa* infection in CF at its June 2013 meeting. The DUSC noted that while the actual number of prescriptions and expenditure for tobramycin solution for inhalation were similar to predicted values, the analysis showed a number of differences in the predicted versus actual patterns of use in practice, in particular with respect to uptake rate and the number of prescriptions per patient.

Methods

Aggregate data from the Highly Specialised Drugs Database was used for data relating to packs, prescriptions and expenditure. Prior to 1 July 2013, most prescriptions supplied through public hospitals only have data available in aggregated form, i.e. the number of packs supplied and cost per quarter. Prescriptions supplied through private hospitals have full data available, however private hospitals account for less than 1 % of packs supplied. Full data for public hospital supply is available from 1 July 2013; however, the data are mostly complete from 1 April 2013. The Department of Human Services (DHS) Supplied Prescriptions Database was used for patient numbers and age.

Results

Analysis of drug utilisation

Patients treated

In the 12 months from May 2013 to April 2014, 1,570 patients received dornase alfa and 106 patients received mannitol on the PBS. This figure may be a slight underestimate for dornase alfa due to a small number of packs supplied (4.12 %) in May 2013 not containing patient level data. Of patients treated with dornase alfa, 9.3 % were aged 5 years or younger.

Packs supplied

Figure 2 presents the number of dornase alfa and mannitol packs supplied by quarter of supply.

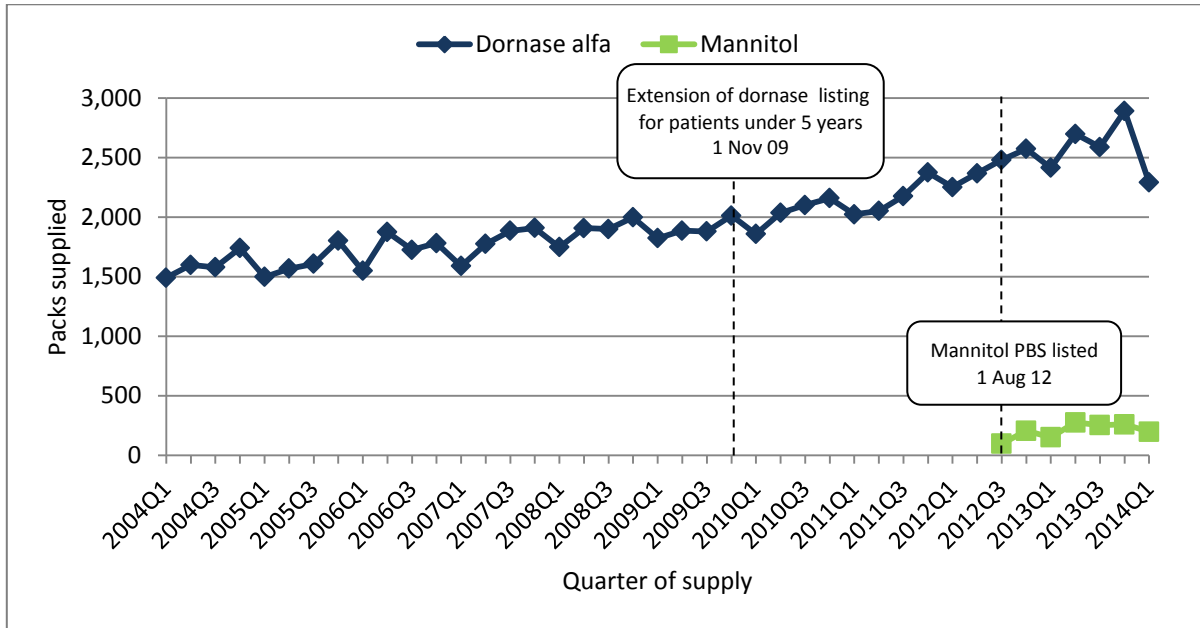


Figure 2: Packs supplied – dornase alfa and mannitol

Source: HSD Database, extracted August 2014

The utilisation of dornase alfa has increased steadily since 2004. The utilisation of mannitol is much less; with less than 300 packs supplied each quarter.

Analysis of expenditure

Figure 3 presents the PBS expenditure on dornase alfa and mannitol by quarter of supply.

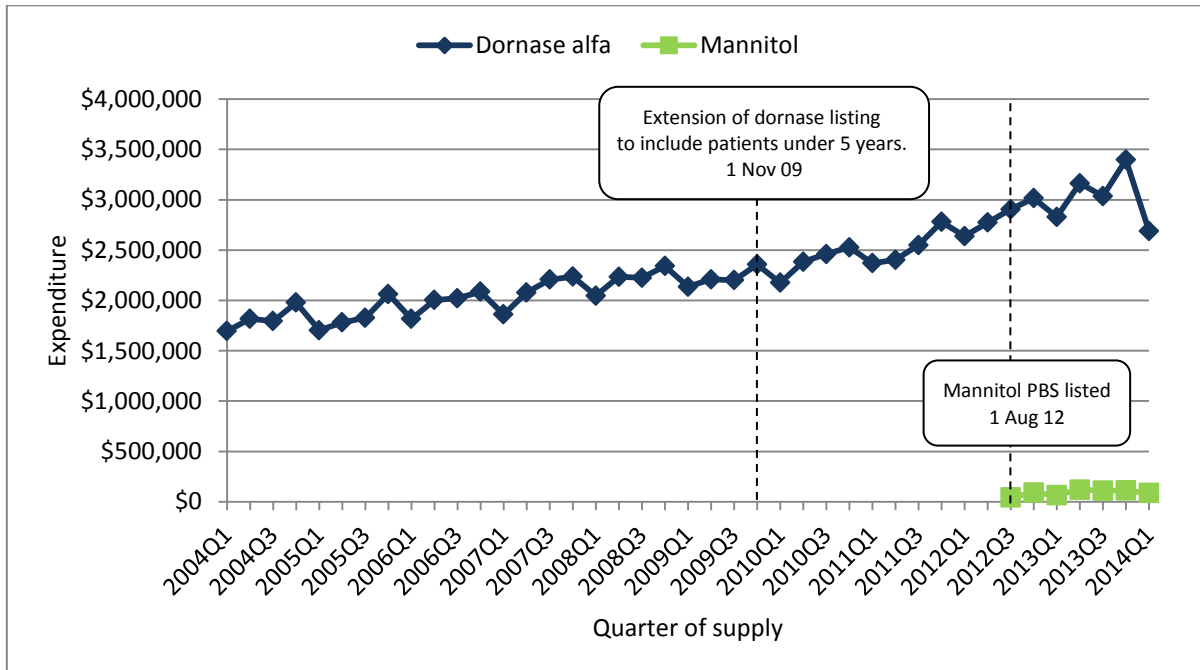


Figure 3: PBS Expenditure – dornase alfa and mannitol

Source: HSD Database, extracted August 2014

In 2013, PBS expenditure was \$12,426,463 for dornase alfa and \$404,442 for mannitol. Dornase alfa expenditure has increased steadily since 2004. Mannitol expenditure is substantially lower, costing less than \$120,000 per quarter since listing. The expenditure is based on the published prices.

Analysis of actual versus predicted utilisation

Table 4 presents the predicted and actual utilisation of mannitol in the first year of listing.

Table 4: Predicted versus actual utilisation of mannitol

	Patients	Packs	Expenditure (published)
Year 1 Predicted	309	8,051	\$2,162,598
Year 1 Actual	106 (May 13- Apr 14)	821	\$352,929
Difference	-65%	-90%	-84%

Source: HSD Database, extracted August 2014 (packs and expenditure); DHS supplied prescriptions database, extracted August 2014 (patients); Mannitol final estimates (predicted values)

Mannitol uptake has been substantially lower than predicted.

Discussion

The utilisation of mannitol in its first year of listing was lower than expected. The DUSC considered this may be due to the requirement for hypersensitivity testing, the recommended dosage consisting of inhalation of 20 capsules per day, patient and clinician preference for hypertonic saline and confusion regarding what constitutes combination use. The DUSC disagreed with the sponsor of mannitol and considered that the hypersensitivity testing protocol may discourage use. The DUSC agreed with the sponsor of mannitol that there may be confusion among clinicians as to what constitutes combination use with dornase alfa, which is not PBS subsidised. It was noted that some patients alternating between therapies may be accessing mannitol through the sponsor's compassionate use program. The DUSC also disagreed with the sponsor that the complexity of the mannitol restriction wording has caused limited uptake, noting that dornase alfa also has a complex restriction. The DUSC considered input from CF clinicians regarding the place in therapy of mannitol may be informative.

The DUSC considered that use of mannitol in Australia may have also been influenced by regulatory concern internationally. The Food and Drug Administration Pulmonary-Allergy Drugs Advisory Committee voted against approval of mannitol in 2013 due to a lack of substantial efficacy data, concerns regarding haemoptysis and concerns regarding the risk-

benefit ratio in children.³ The FDA Pulmonary-Allergy Drugs Advisory Committee required an additional Phase III trial to further support mannitol's risk-benefit ratio. The sponsor advises that this trial commenced recruitment in 2014. Mannitol received marketing authorisation by the European Medicines Agency in 2012.⁴

The utilisation of dornase alfa has steadily increased since 2004. In the most recent year of data, 9.3 % of patients were aged 5 years or less.

A co-administration analysis examining the use of dornase alfa with mannitol was not undertaken due to low utilisation of mannitol and limited patient level data for HSD Program medicines to undertake this analysis.

DUSC actions

- The DUSC requested that a copy of the report be provided to the Post-Market Review of Authority Required PBS listings noting that dornase alfa and mannitol are infrequently prescribed in private hospitals and that these are Authority required items that require prior approval to prescribe, whereas public hospitals have an Authority required (streamlined) listing.
- The DUSC requested that the Secretariat seek advice from CF clinicians regarding the place in therapy of mannitol, the potential clinician confusion regarding the cycling of treatments and the low uptake of mannitol.
- The DUSC requested that the report, together with advice from CF clinicians, be provided to the PBAC for action. The DUSC considered the PBAC may wish to provide further guidance on combination therapy of mannitol and dornase alfa, including whether a major or minor submission would be needed.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

³ Food and Drug Administration. Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting - January 30, 2013. Silver Spring, USA; 14 February 2013. Available from: <<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM340156.pdf>>. Accessed 1 September 2014.

⁴ European Medicines Agency. European public assessment reports - Bronchitol (mannitol). London, UK. European Medicines Agency; 16 February 2012. Available from <<http://www.ema.europa.eu/ema/>>. Accessed 1 September 2014.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Pharmaxis Ltd: The sponsor thanks DUSC for its analysis, and looks forward to working together with the PBAC.

Roche Products Pty Ltd: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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