PUBLIC SUMMARY DOCUMENT
Product: Mannitol, capsule containing powder for oral inhalation, 40 mg (for use in inhaler device), Bronchitol®
Sponsor: Pharmaxis Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application
The submission sought a Section 100 (Highly Specialised Drug) PBS listing for the treatment of cystic fibrosis (CF) in both paediatric (six years and above) and adult populations as either add on therapy to dornase alfa or in patients intolerant to, or inadequately responsive to dornase alfa.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background
This drug had not previously been considered by the PBAC.

3. Registration Status
Mannitol powder for inhalation (Bronchitol®) was TGA registered on 11 March 2011 for the treatment of cystic fibrosis (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.

4. Listing Requested and PBAC’s View
The submission proposed two listings, option A and B.

Option A
Section 100 (Highly Specialised Drugs)

Bronchitol is indicated for the treatment of cystic fibrosis (CF) in both paediatric and adult populations six years and above as either add-on therapy to dornase alfa or in patients intolerant of or inadequately responsive to dornase alfa

Private Hospital Authority Required
Use by cystic fibrosis patients who satisfy all of the following criteria:
(1) are 6 years of age or older;
(2) have a FEV1 greater than 30% predicted for age, gender and height
(3) are on dornase alfa or are intolerant or inadequately responsive to dornase alfa
(4) have evidence of chronic suppurative lung disease (cough and sputum most days of the week, or greater than 3 respiratory tract infections of more than 2 weeks' duration in any 12 months, or objective evidence of obstructive Airways disease);

Private hospital authority required
PATIENTS WHO ARE NOT CURRENTLY ON DORNASE ALPHA

Treatment of cystic fibrosis patients who:
(i) have previously trialled and not met subsidisation criteria for dornase alfa
(ii) Are intolerant to dornase alfa
(iii) Do not continue dornase alfa after clinical assessment
In order for patients to be eligible for participation in the HSD program, the following conditions must be met:

1. Patients must be assessed at cystic fibrosis clinics/centres which are under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis and the prescribing of mannitol powder for inhalation therapy under the HSD program is limited to such physicians. If attendance at such units is not possible because of geographical isolation, management (including prescribing) may be by specialist physician or paediatrician in consultation with such a unit;

2. The measurement of lung function is to be conducted by independent (other than the treating doctor) experienced personnel at established lung function testing laboratories, unless this is not possible because of geographical isolation;

3. Prior to mannitol powder for inhalation therapy, a baseline measurement of FEV1 must be undertaken during a stable period of the disease;

4. Patients must be assessed for bronchial hyperresponsiveness as per TGA approved PI Mannitol Tolerance Test. If the patient has a positive hyperresponsiveness test they must not be prescribed Mannitol powder for inhalation. Patients with negative tests may commence mannitol powder for inhalation therapy.

5. Initial therapy is limited to 4 weeks’ treatment with Bronchitol at 400 mg BD;

6. At or towards the end of the initial 4 weeks' trial, patients must be reassessed and a further FEV1 measurement be undertaken (single test under conditions as above). Patients who achieve a 10% or greater improvement in FEV1 (compared to baseline established prior to mannitol for inhalation treatment) are eligible for continued subsidy under the HSD program at a dose of 400mg BD;

7. Patients who fail to meet a 10% or greater improvement in FEV1 after the initial 4 weeks' treatment at a dose of 400mg BD, may have 1 further trial in the next 12 months but not before 3 months after the initial trial;

8. Following an initial 6 months’ therapy, a global assessment must be undertaken involving the patient, the patient's family (in the case of paediatric patients) and the treating physician(s) to establish that all agree that mannitol powder for inhalation treatment is continuing to produce worthwhile benefits. (Mannitol powder for inhalation therapy should cease if there is not general agreement of benefit as there is always the possibility of harm from unnecessary use.) Further reassessments are to be undertaken at six-monthly intervals;

9. Other aspects of treatment, such as physiotherapy, must be continued;

Note:
It is highly desirable that all patients be included in the national cystic fibrosis patient data-base.

Private hospital authority required

TREATMENT OF CYSTIC FIBROSIS PATIENTS CURRENTLY TAKING DORNASE ALFA

In order for patients to be eligible for participation in the HSD program, the following conditions must be met:

1. Patients must have been taking dornase alfa for at least 6 months;

2. Following an initial 6 months’ therapy of dornase alfa, a global assessment must be undertaken involving the patient, the patient's family (in the case of paediatric patients) and the treating physician(s) to establish that all agree that greater improvement in FEV1 could be achieved with the addition of mannitol powder for inhalation. (Mannitol powder for inhalation therapy should not be commenced if there is not general agreement that greater FEV1 improvement could be attained or if there is a possibility of harm from unnecessary use.) Further reassessments are to be undertaken at six-monthly intervals;

3. The measurement of lung function is to be conducted by independent (other than the treating doctor) experienced personnel at established lung function testing laboratories, unless this is not possible because of geographical isolation;

4. Prior to mannitol for inhalation therapy, a baseline measurement of FEV1 must be undertaken during a stable period of the disease;

5. Patients must be assessed for bronchial hyperresponsiveness as per TGA approved PI Mannitol Tolerance Test. If the patient is hyperresponsive to mannitol they must not be prescribed Mannitol powder for inhalation. Patients with negative tests may commence mannitol powder for inhalation therapy.

6. Initial therapy is limited to 4 weeks’ treatment with Bronchitol at 400mg BD;

7. At or towards the end of the initial 4 weeks' trial, patients must be reassessed and a further FEV1 measurement be undertaken (single test under conditions as above). Patients who achieve a 10% or greater improvement in FEV1 (compared to first line dornase alfa therapy [established prior to mannitol for inhalation therapy]) are eligible for continued subsidy under the HSD program at a dose of 400mg BD;
treatment) are eligible for continued subsidy under the HSD program at a dose of 400mg BD;
(7) Patients who fail to meet a 10% or greater improvement in FEV\(_1\) (compared to first line dornase alpha therapy baseline after the initial 4 weeks' treatment at a dose of 400mg BD, may have 1 further add on trial in the next 12 months but not before 3 months after the initial trial;
(8) Other aspects of treatment, such as physiotherapy, must be continued;

**Note:**
It is highly desirable that all patients be included in the national cystic fibrosis patient data-base.

**Option B**

**Section 100** (Highly Specialised Drugs)

Bronchitol is indicated for the treatment of cystic fibrosis (CF) in both paediatric and adult populations six years and above s either add-on therapy to dornase alpha or in patients intolerant of or inadequately responsive to dornase alfa.

**Private Hospital Authority Required**

Use by cystic fibrosis patients who satisfy all of the following criteria:
(1) are 6 years of age or older;
(2) are on dornase alfa or are intolerant or inadequately responsive to rhDNase

**Private hospital authority required**

**PATIENTS WHO ARE NOT CURRENTLY ON DORNASE ALPHA**

Treatment of cystic fibrosis patients who;
(i) have previously trialled and not met subsidisation criteria for Dornase alpha
(ii) are intolerant to dornase alfa
(iii) do not continue dornase alfa after clinical assessment

In order for patients to be eligible for participation in the HSD program, the following conditions must be met:
(1) Patients must be assessed at cystic fibrosis clinics/centres which are under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis and the prescribing of mannitol powder for inhalation therapy under the HSD program is limited to such physicians. If attendance at such units is not possible because of geographical isolation, management (including prescribing) may be by specialist physician or paediatrician in consultation with such a unit;
(2) The measurement of lung function is to be conducted by independent (other than the treating doctor) experienced personnel at established lung function testing laboratories, unless this is not possible because of geographical isolation;
(3) Patients must be assessed for bronchial hyperresponsiveness as per TGA approved PI Mannitol Tolerance Test. If the patient has a positive hyperresponsiveness test they must not be prescribed Mannitol powder for inhalation. Patients with negative tests may commence mannitol powder for inhalation therapy.
(4) Following an initial 6 months' therapy, a global assessment must be undertaken involving the patient, the patient's family (in the case of paediatric patients) and the treating physician(s) to establish that all agree that mannitol powder for inhalation treatment is continuing to produce worthwhile benefits. (Mannitol powder for inhalation therapy should cease if there is not general agreement of benefit as there is always the possibility of harm from unnecessary use.) Further reassessments are to be undertaken at six-monthly intervals;
(5) Other aspects of treatment, such as physiotherapy, must be continued;

**Note:**
It is highly desirable that all patients be included in the national cystic fibrosis patient data-base.

**Private hospital authority required**

**TREATMENT OF CYSTIC FIBROSIS PATIENTS CURRENTLY TAKING DORNASE ALFA**

In order for patients to be eligible for participation in the HSD program, the following conditions must be met:
(1) Patients must have been taking dornase alfa for at least 6 months;
(2) Following an initial 6 months' therapy of dornase alfa, a global assessment must be undertaken involving the patient, the patient's family (in the case of paediatric patients) and the treating physician(s) to establish that all agree that greater improvement in FEV\(_1\) could be achieved with the addition of mannitol powder for inhalation. (Mannitol powder for inhalation therapy should not be commenced if there is not general agreement
that greater FEV1 improvement could be attained or if there is a possibility of harm from unnecessary use.)
Further reassessments are to be undertaken at six-monthly intervals;
(3) The measurement of lung function is to be conducted by independent (other than the treating doctor)
experienced personnel at established lung function testing laboratories, unless this is not possible because of
geographical isolation;
(4) Patients must be assessed for bronchial hyperresponsiveness as per TGA approved PI Mannitol Tolerance
Test. If the patient is hyperresponsive to mannitol they must not be prescribed Mannitol powder for inhalation.
Patients with negative tests may commence mannitol powder for inhalation therapy.
(5) Other aspects of treatment, such as physiotherapy, must be continued;

Note:
It is highly desirable that all patients be included in the national cystic fibrosis patient data-base.

For PBAC’s view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Cystic fibrosis (CF) is a common hereditary disease which affects the entire body, causing
progressive disability and often early death. CF is caused by a mutation in the gene for the
protein cystic fibrosis transmembrane conductance regulator (CFTR). This gene is required to
regulate the components of sweat, digestive juices, and mucus.

The aim of treatment of CF is to alleviate symptoms, improve quality of life and to slow the
decline in lung function. This is achieved by improving airway clearance, by eradicating or
suppressing the growth of bacterial pathogens and attenuating airway inflammation.

By mid childhood, most patients have increased airway secretions, and enhancing mucus
clearance is a major goal of therapy. Several strategies have been proven to be effective,
including physiotherapy, local hydration with inhaled moisture, enzymes to break down the
inflammatory cell products, anti-inflammatory agents and aggressive treatment of bacterial
infections. In a proportion of patients, mucolytic agents are prescribed. Currently dornase
alfa is the only mucolytic agent subsidised on the PBS for use in CF.

The submission proposed that the place in therapy of mannitol powder for inhalation is either
as add on therapy to dornase alfa or as an alternative therapy for patients 6 years of age or
older intolerant or inadequately responsive to dornase alfa.

6. Comparator
The submission presented two comparators for dry powder for inhalation (DPI) mannitol
based on whether DPI mannitol is used as a monotherapy or add-on therapy:

• For patients who are intolerant or unresponsive to dornase alfa the submission
nominated a comparison between DPI mannitol monotherapy vs. re-trial with dornase
alfa.

This was not accepted by the PBAC.

• For patients who have an inadequate response to dornase alfa the submission
nominated a comparison between dornase alfa plus DPI mannitol add-on therapy vs.
dornase alfa alone.

For PBAC’s view, see Recommendation and Reasons.
7. **Clinical Trials**

The submission presented one head-to-head cross-over trial of DPI mannitol vs. dornase alfa vs. DPI mannitol and dornase alfa combination in children with cystic fibrosis (CF-203, n=26)).

The submission also presented two trials of DPI mannitol vs. a sub-therapeutic dose of mannitol as control (CF-301, n=295; CF-302, n=305) and one trial of dornase alfa vs placebo (Fuchs *et al.* 1994) in children and adults with cystic fibrosis.

For the comparison of DPI mannitol as add-on to dornase alfa vs dornase alfa alone, trials CF-301/CF-302 included predefined subgroup analyses of patients on concomitant use of dornase alfa; ie those patients on dornase alfa at baseline continue to use dornase alfa during the trial.

The table below details the published trials presented in the submission:

<table>
<thead>
<tr>
<th>Trial ID/ First author</th>
<th>Protocol title/ Publication title</th>
<th>Publication citation</th>
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8. **Results of Trials**

Direct comparison (CF-203, n=26)

Based on the key outcomes (FEV₁, protocol defined pulmonary exacerbation (PDPE) events and quality of life(QOL)) reported in the head-to-head cross-over trial of DPI mannitol vs. dornase alfa vs. DPI mannitol/dornase alfa combination (CF-203) the PBAC noted that there were no statistically significant differences in lung function (as measured by FEV₁ and FVC, FEV₁/FVC, FEF₂₅₋₇₅, PEF), PDPE events or respiratory quality of life scores between treatment groups.

The PBAC acknowledged that trial CF-203 was underpowered and the larger trials of CF-301/CF-302, which had subgroups of patients on either both treatments or mannitol monotherapy, did not show a consistent trend of patients performing worse when the using mannitol in combination with dornase alfa, the benefit of mannitol as an add-on therapy remains uncertain.

**DPI mannitol vs. control (sub-therapeutic mannitol) (CF-301/CF-302)**
The main FEV₁ results from the CF-301/CF-302 trials were reported as either the mean change from baseline to Week 26 or as the overall change from baseline averaged over the Week 6, 14 and 26 time points. The submission presented both sets of results and a meta-analysis using the mean change in FEV₁ from baseline to Week 26. For consistency, the meta-analysis was conducted during the evaluation using the overall change (Week 6-26) in FEV₁ from baseline.

The PBAC noted that DPI mannitol was associated with statistically significant short-term (26 week) improvements in lung function (FEV₁) compared to control in the total CF-301/CF-302 populations (approximately 2-4% absolute FEV₁ improvement depending on measure).

The key spirometry outcomes reported in the dornase alfa users/non-users subgroups of the DPI mannitol vs. control trials (CF-301, CF-302) showed that DPI mannitol treatment was associated with a statistically significant improvement in lung function compared to control both in patients receiving concomitant dornase alfa (overall FEV₁ change 3.20%, p = 0.014) and in patients not receiving concomitant dornase alfa (overall FEV₁ change 4.65%, p = 0.007).

The key clinical outcomes reported in the total populations of the DPI mannitol vs. control trials (CF-301, CF-302) were mean annualised rate of PDPE and PE events per patient.

The PBAC noted that there were no statistically significant differences in exacerbation rates, use of rescue antibiotics or hospitalisations between DPI mannitol and control in the CF-301/CF-302 populations. There was also no statistically significant difference in exacerbation rates between DPI mannitol and control in patients using concomitant dornase alfa.

DPI mannitol treatment was associated with a statistically significant decrease in protocol defined pulmonary exacerbation (PDPE) rates compared to control in patients that were not using concomitant dornase alfa (rate ratio 0.48; 95% CI 0.23, 0.99), although the wide confidence intervals raise uncertainty on the magnitude of effect. There was no statistically significant difference in PE rates between treatment groups.

The sponsor provided in its Pre-PBAC response an analysis of the proportion of patients with PDPE events for the pooled data of CF-301 and CF-302 (to allow comparison to other studies).

**Indirect comparison (CF-301/CF-302 vs. Fuchs 1994)**

The outcomes of the indirect comparison are change in FEV₁ (%) from baseline and risk of PDPE events.

Based on the indirect analyses, the submission claimed DPI mannitol and dornase alfa were comparable in terms of improving lung function and reducing the risk of exacerbations.

The PBAC noted that the outcome of change in FEV₁ from baseline differed between trials. Results from the CF-301 and CF-302 trials were based on the mean change in FEV₁ from
baseline to Week 26 (end of the study) while the results from the Fuchs et al (1994) trial were based on the overall change in \( \text{FEV}_1 \) from baseline averaged across multiple time points throughout the study (4, 8, 12, 16, 20 and 24 weeks).

The outcome of risk of PDPE events differed between trials. Results from the CF-301 and CF-302 are based on the annualised rate of PDPE events while the results from the Fuchs et al (1994) trial are based on the proportion of patients with PDPE events adjusted for baseline differences in age between treatment arms.

The PBAC also noted the common comparator arms were not the same; the DPI mannitol trials (CF-301/CF-302) had sub-therapeutic dose of mannitol in the control arm and potential concomitant use of dornase alfa, whereas the dornase alfa trial (Fuchs) had a placebo control.

For PBAC’s view, see Recommendation and Reasons.

The PBAC noted that similar proportions of patients in the DPI mannitol and control (sub-therapeutic mannitol) treatment arms experienced adverse events during the CF-301/CF-302 trials. Patients were more likely to experience treatment-related events in the DPI mannitol arm (mainly cough and haemoptysis) compared to control. In the CF-301 trial, DPI mannitol was associated with a higher incidence of withdrawals due to adverse events compared to placebo (16% vs. 8%). There were no published long-term safety data on DPI mannitol beyond the 6 month timeframe of the clinical trials.

Adverse events associated with dornase alfa include: voice alteration, rash, haemoptysis, dyspnoea, pharyngitis and laryngitis. There were insufficient data to assess whether DPI mannitol and dornase alfa have comparable safety profiles.

9. Clinical Claim

Monotherapy for patients who are intolerant or unresponsive to dornase alfa (comparator retriol of dornase alfa):

The submission claimed DPI mannitol as being similarly effective to dornase alfa with a similar safety profile to dornase alfa.

Add-on therapy to dornase alfa for patients who have an inadequate response to dornase alfa (comparator is placebo as add-on to dornase alfa):

The submission claimed that DPI mannitol is more effective than placebo/control at improving \( \text{FEV}_1 \) outcomes in subjects with cystic fibrosis either as monotherapy or when used in combination with dornase alfa. DPI mannitol had higher rates of adverse events related to treatment and higher rates of withdrawal due to adverse events than placebo/control.

For the PBAC’s view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented two economic evaluations:

Monotherapy:

- A cost-minimisation analysis of DPI mannitol monotherapy compared to dornase alfa.

Add-on:
A modelled cost utility analysis of dornase alfa with DPI mannitol add-on therapy compared with dornase alfa alone.

Cost minimisation (DPI mannitol monotherapy vs. dornase alfa monotherapy)

The submission claimed that DPI mannitol (400 mg twice a day) is equivalent to dornase alfa (2.5 mg once a day) based on the daily dose used in the included trials.

The comparative cost of DPI mannitol was less than dornase alfa.

Cost effectiveness (dornase alfa with DPI mannitol add-on therapy vs. dornase alfa)

The submission presented an economic model that compared the costs and health outcomes associated with usual care, DPI mannitol alone, dornase alfa alone, and the combination of DPI mannitol with dornase alfa in patients with cystic fibrosis.

The submission assumed that the combined results of the control arms of studies CF-301/CF-302 (which compared DPI mannitol to sub-therapeutic mannitol) could represent the efficacy of dornase alfa alone in the economic model.

The economic model assumed that the short-term (26 week) improvement in lung function (FEV₁) associated with DPI mannitol treatment compared to control would be maintained beyond the clinical trial duration.

The model assumed that DPI mannitol treatment would reduce exacerbations compared to control. The risk of exacerbations was a key driver of the economic model. An incremental cost per quality adjusted life year gained was calculated to be between $45,000-$75,000.

The results of the sensitivity analyses indicated that the model was most sensitive to continuation rules, price of DPI mannitol and the risk of exacerbations. The sensitivity analyses presented in the submission suggested that removing the continuation rule or increasing the requirement to a 10% FEV₁ improvement will lead to higher ICERs compared to the base case (5% FEV₁ improvement).

The PBAC noted that the clinical trial data presented in the submission did not show a statistically significant reduction in exacerbations with DPI mannitol add-on therapy. Assuming that patients treated with DPI mannitol have the same risk of exacerbation as control patients this increased the ICER from to between $75,000-$105,000 per QALY.

For PBAC’s view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications
The financial cost per year to the PBS was estimated by the submission to be less than $10 million in the fifth year of listing. The PBAC considered this an overestimate as the submission did not include the proposed continuation rules in its estimates and did not include any cost-offsets due to drug substitution.

12. Recommendation and Reasons
The PBAC considered the clinical place of mannitol was uncertain. The PBAC noted a clinician’s comments at the hearing regarding the place of mannitol in CF therapy. The clinician’s comments did not support the pre-PBAC response which suggested that the place of mannitol would be as a ‘last resort’ when other treatment options had failed. The clinician suggested that a PBS listing for mannitol was appealing as it provides a unique option for treatment of CF which does not require nebulisation. Whilst sympathetic with the notion of CF patients looking for alternatives to nebulised forms of treatment, the PBAC considered the twice daily regimen for mannitol of 10 capsules via inhaler, with 5-15 minutes of bronchodilator prior to use, was complex and intensive, particularly for children, and could possibly result in reduced compliance.

The ACPM recommendation for use of mannitol in second-line reflects the sponsor’s proposed listing, however, trial data show there may be broader use for mannitol in CF.

The proposed comparator of a re-trial of dornase alfa, in patients intolerant or unresponsive to dornase alfa, was not accepted. Patients not responding to dornase alfa would not be likely to try it again, nor would they qualify under the continuation criteria for dornase alfa. Placebo, or hypertonic saline should have been considered relevant comparators. The clinician considered mannitol to be sufficiently different to hypertonic saline due to the different forms of administration. However, the PBAC did not accept the unique delivery mechanism of mannitol as a sufficient reason to exclude hypertonic saline as a relevant comparator.

The PBAC questioned the applicability of the trial populations to the proposed PBS listings and overall, considered the evidence to support the proposed listings was uncertain. Dornase alfa and mannitol have separate mechanisms of action. The PBAC was not convinced that combination use of these drugs would not lead to worse outcomes. Although acknowledging that trial CF-203 was underpowered and the larger trials of CF-301/CF-302, which had subgroups of patients on either both treatments or mannitol monotherapy, did not show a consistent trend of patients performing worse when the using mannitol in combination with dornase alfa, the benefit of mannitol as an add-on therapy remains uncertain. Trial data also did not support the monotherapy listing for patients who had failed to achieve an adequate response to dornase alfa. The indirect comparison with Fuchs (1994) is highly uncertain because of a lack of exchangeability and differences in the outcome measures between the trials.

There were no statistically significant differences in exacerbation rates, use of rescue antibiotics, or hospitalisations between mannitol and control in CF-301/CF-302 populations. There was also no statistically significant difference in exacerbation rates between mannitol and control in patients using concomitant dornase alfa.

The economic model to support the proposed add-on restriction resulted in a high and uncertain ICER. The model was dependent on a number of assumptions (e.g. reduction in exacerbation events, maintenance of treatment effect) that were not well justified in the submission. The key source of uncertainty was the use of different exacerbation rates between mannitol and control in the model when this was not demonstrated to be statistically significant in the trials. Given the use of dornase alfa in some, but not all patients in the two key trials, the data used in the model was not appropriate.
The cost-minimisation in the monotherapy setting remained highly uncertain, even with the offer a lower price than dornase alfa.

The PBAC therefore rejected the submission because the comparator when dornase alfa has failed was inappropriate and because of uncertain effectiveness and resulting uncertain cost effectiveness, when used in combination with dornase alfa.

The PBAC also acknowledged and noted the consumer comments on this item.

**Recommendation:**
Reject

13. **Context for Decision**
The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. **Sponsor’s Comment**
Pharmaxis believes that a lack of available prescribing data has lead to misunderstandings and incorrect conclusions on how existing therapies are used in cystic fibrosis. Pharmaxis is now working with the CF community to provide evidence on current use of CF treatments to allow a better assessment of the true place of Bronchitol in therapy, and an appropriate comparator for patients who are not responding to currently available treatments.