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Horizon Scanning Technology Prioritising Summary

eFlow® Rapid neubliser for the treatment of patients with cystic fibrosis

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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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This Horizon scanning prioritising summary was prepared by Linda Mundy and Professor Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, School of Population Health and Clinical Practice, Mail Drop DX 650 545, University of Adelaide, Adelaide, SA, 5005.

PRIORITISING SUMMARY

REGISTER ID: **000485 (REFERRAL)**

NAME OF TECHNOLOGY: **EFLOW® RAPID NEBULISER**

PURPOSE AND TARGET GROUP: **FOR THE TREATMENT OF PATIENTS WITH CYSTIC FIBROSIS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☒	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☒	Yes	ARTG number 149078 eFlow Rapid 148661 eFlow
☐	No	
☐	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		✓
The Netherlands	✓		
France	✓		
Canada	✓		
Australia		✓	

IMPACT SUMMARY:

Pari Pharma GmbH (Germany) provides the eFlow® Rapid nebuliser (ARTG number 149078) with the aim of delivering medication in an aerosol form. The Pari eFlow® (ARTG number 148661), although registered on the TGA is currently only in use under clinical trial conditions using a specific pharmaceutical in conjunction with the nebuliser. The technology is available direct from the distributer, Technipro-PulmoMed Pty Ltd (New South Wales), primarily for patients with cystic fibrosis but may be used for patients with an upper respiratory disease or severe asthma. The Pari

eFlow® Rapid nebuliser was approved for use by the United States FDA in 2004 and for European markets in 2005 (Rottier et al 2009).

BACKGROUND

Cystic fibrosis (CF) is a recessive genetic disorder caused by defects in the cystic fibrosis transmembrane regulator (CTFR) gene. This genetic defect affects the glands which produce body secretions such as sweat, mucus and enzymes and although it may affect many organs in the body, it primarily affects the lungs, pancreas, intestines and the reproductive system. The CTFR gene is responsible for salt transport across cell membranes; as a consequence of the genetic defect, the mucus of people with CF is thick and viscous. When the thick and sticky mucus accumulates in the patient's lungs it becomes difficult to shift. CF patients develop a persistent cough to help clear away mucus build-up in the lung. However, the mucus creates a breeding ground for bacteria and other infections and recurrent infections lead to irreversible lung tissue scarring (Al-Yaman et al 2002). There is no cure for CF and current therapies aim to slow the progression of the disease. CF patients require lifelong intensive treatment including physiotherapy, antibiotic treatment, dietary control and digestive enzyme capsules. Patients with CF have a shortened life expectancy, with the predominant cause of death being loss of lung function, which begins in infancy and continues throughout the patient's life (Cystic Fibrosis Australia 2009b).

The Pari eFlow Rapid is a small (fits in the palm of your hand), light weight, portable nebuliser, which is capable of efficiently producing aerosols from liquid medications, such as antibiotics, via a vibrating, perforated membrane (Figure 1).

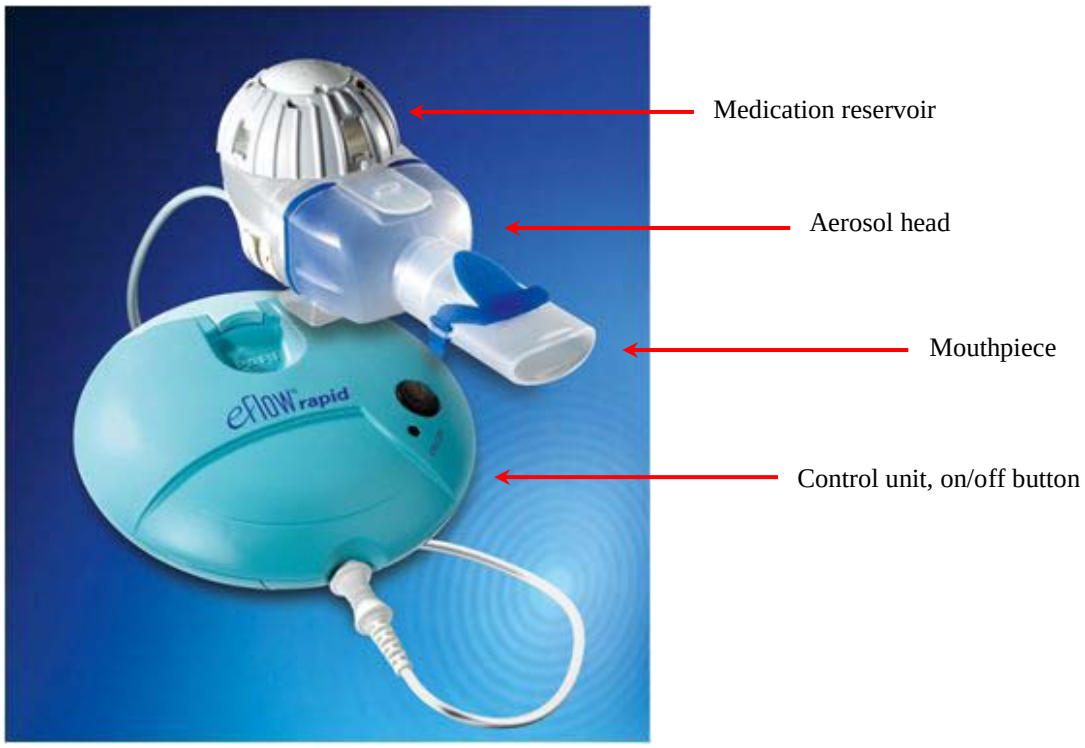

Figure 1 The Pari eFlow® Rapid nebuliser (printed with permission Pari Pharma)

The device is electronic and therefore quieter than conventional compressor type nebulisers. The device can operate via a charged battery or mains supply. The dimensions of the nebuliser and controller are 140 x 50 x 63mm and 117 x 42mm, respectively. The eFlow® Rapid comes supplied with two aerosol heads allowing one to be used whilst the other one is cleaned (PARI GmbH 2008). The eFlow® Rapid produces aerosols with a very high density of an active drug with a defined droplet size and results in shorter treatment times compared to than conventional nebulisers. The eFlow® Rapid uses a vibrating mesh which determines the size of the inhaled particles. It has been suggested that new nebuliser devices such as the eFlow® Rapid increase the deposition of antibiotic therapy into the lungs with improved patient outcomes which ultimately result in increased patient compliance (Traini & Young 2009).

The principle underlying the eFlow® Rapid is similar to that of an ink-jet printer, in that the liquid medication is in contact with the micro-perforated membrane, with the opposing side of the membrane open to the air. Around the membrane the pressure in the liquid is built up causing the fluid to be pushed through holes in the membrane in uniform sized droplets, creating an aerosol. Acoustic pressure, generated by the high-frequency vibration of the membrane, drives the aerosol outwards more efficiently than a non-vibrating, passive membrane (Lass et al 2006).

The majority of CF patients use antibiotic therapy in some form. In 2008, of the 95 per cent of patients who had this information recorded, 73 per cent had antibiotic therapy. Oral antibiotics were used by 91 per cent of these patients and of these, 41 per cent used oral antibiotics continuously rather than as needed. Inhaled antibiotics were used by 53 per cent of CF patients with 25 per cent using them on a continuous basis. Of the patients on the CF register, 288 received intravenous antibiotic therapy either in the home (n=92) or in hospital and at home (n=196). Three or more courses of IV antibiotics were received by 49 patients (Cystic Fibrosis Australia 2010). Other therapies used include pancreatic enzymes, vitamin supplements, bronchodilators, long-term oxygen therapy and non-invasive ventilation (Cystic Fibrosis Australia 2010).

Delivery of antibiotics via the inhaled route is advantageous for respiratory tract infections as the lungs are directly targeted and the therapeutic dose is lower than that needed via the oral or systemic routes of delivery. In addition, the inhaled route is more suitable for some antibiotics which are not suitable for delivery via the oral route due to poor bio-availability (Traini & Young 2009). Issues to be taken into account when considering delivering a pharmaceutical via the inhaled route is that the properties of the drug must remain unchanged following the nebulisation process. In addition the pH and osmolarity of the nebulised solution need to be finely balanced to prevent coughing and bronchospasms in the patient. The aerosol droplets are usually 1-5 μm in diameter and total treatment time should be less than 15 minutes (Hureaux et al 2009).

Consideration when choosing the type of device for the inhalation of medications must be given to the particle mass (fraction of the nominal dose that leaves the inhaler), the inhaled mass (the fraction that is actually inhaled by the patient) which may differ dramatically between nebulisers and the respirable mass or the fine particle fraction, which is the proportion of the inhaled mass that is small enough (1-5µm) to bypass the upper airways and deposit in the lower airways (Heijerman et al 2009).

Most nebulised drugs are either solutions that contain a drug dissolved in saline or a suspension of a non-soluble drug. The use of aerosol delivery by means of nebulisation may increase the number of therapeutic options available to CF patients as previously insoluble, but highly effective, drugs such as rifampicin may now be successfully used. A great number of clinical trials are currently underway or recently completed aimed at identifying the most effective drugs for inhalation for the treatment of CF. The eFlow® (rather than the eFlow® Rapid) is being assessed for use with a number of developmental antimicrobials including aztreonam, levofloxacin and liposomal amikacin (Traini & Young 2009).

CLINICAL NEED AND BURDEN OF DISEASE

One in twenty five of Caucasian Australians are carriers of the CF genetic defect. As the disease is recessive two copies of the defective gene are required, therefore both parents need to be carriers to produce a CF baby. Two carriers have a 25 per cent chance of their child having CF, a 50 per cent chance of producing a carrier and a 25 per cent chance of producing a normal child (Figure 2). Australia has a nationwide neonatal screening program that identifies approximately 95 per cent of CF babies. In addition, antenatal screening exists for subjects who have a CF family history or for partners of known CF patients (Cystic Fibrosis Australia 2009b).

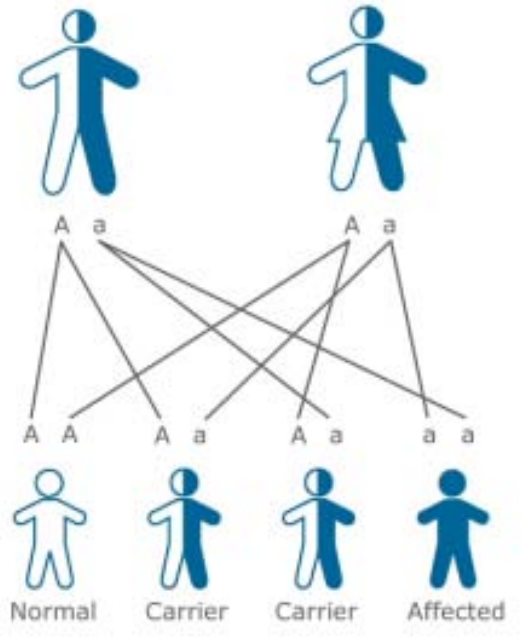

Figure 2 The inheritance of the cystic fibrosis genetic defect

In 2008, there were 2,843 persons living with CF in Australia, with a mean age of 18.7 years (median 17 years). During that year, 73 infants were diagnosed with CF at a median age of 1.5 months, with 62 diagnosed at less than one year. Of the total number of patients on the CF register, one in six individuals also had siblings with CF. During this same period, 19 individuals died from CF at a mean age of 30.2 years (Cystic Fibrosis Australia 2010). Gains from early screening and better management include an improved life expectancy for people with cystic fibrosis. Comparisons of median age at death from cystic fibrosis in 10 countries (including Australia) showed an increase in the median age at death from eight years in 1974 to 21 years in 1994 (Al-Yaman et al 2002). With the availability of improved treatment regimes, the average life expectancy of a patient with CF in Australia is now mid to late thirties with most patients expected to reach adulthood (Figure 3) (Cystic Fibrosis Australia 2009b).

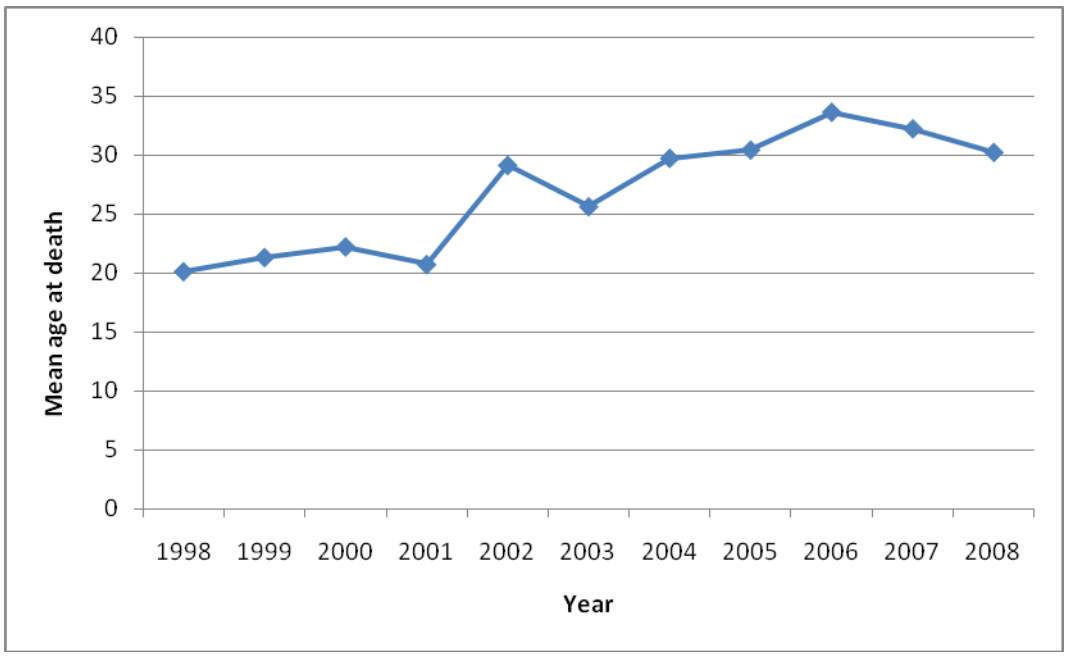

Figure 3 Mean age of death from cystic fibrosis (based on data from (Cystic Fibrosis Australia 2010)

Public hospital separation data for cystic fibrosis was difficult to obtain. Definitions for the Australian Refined Diagnosis Related Groups (AR-DRG) changed in 2004-05 from version 4 to version 5. In 2004-05, there were two AR-DRG numbers for cystic fibrosis, E60A and E60B for cystic fibrosis with and without catastrophic or severe complication and/or comorbidities, respectively. During this period, for each of these AR-DRGs there were 1,985 and 991 public hospital separations, associated with an average length of stay of 12.3 and 7.5 days, respectively. The overwhelming number of these separations occurred in patients less than 29 years of age (78-84%), with the peak of separations occurring in the 10-19 year age bracket (34-40%) (AIHW 2010). More recent data could not be obtained as E60A and B were not listed in version 5.0 of the AR-DRG on the AIHW data site. During 2008, the average number of visits for

children and adolescents to a CF outpatient clinic was 4.8 (median 4) and for adults 5.8 (median 5). According to data obtained from the CF register, 51.7 per cent of all CF patients were hospitalised at least once during 2008. Nearly two per cent of patients were hospitalised more than six times in 2008. The majority of hospitalisations were for respiratory causes (Cystic Fibrosis Australia 2010).

During 2008, 69 per cent of CF patients had at least two sputum samples analysed for infection. Of those patients tested, 53 per cent were positive for Pseudomonas, with 38 per cent of these positive for *Pseudomonas aeruginosa*. The prevalence of Pseudomonas infection is lower in children than in adults, young children with CF are more likely to be positive for *Staphylococcus aureus* infection than adults. *Haemophilus influenzae* was also present in a high proportion of children, with 25 and 23 per cent of children aged 0-4 and 5-9 years infected, respectively. Thirteen per cent of children aged 0-4 years were also infected with *Escherichia coli* (Cystic Fibrosis Australia 2010).

In New Zealand, rates of CF are similar as to those in Australia with approximately one in 25 New Zealanders of Caucasian origin being a carrier. CF is rare in Polynesians. Of all births in New Zealand, approximately one in 3000 to 3,500 infants will be born with CF. Currently there are more than 400 children and adults living with CF in New Zealand (Cystic Fibrosis Association of New Zealand 2010). No other data from New Zealand could be identified.

DIFFUSION

Approximately 5-600 eFlow® Rapid nebulisers have been sold direct to patients in Australia (personal communication Technipro-PulmoMed Pty Ltd).

COMPARATORS

The main treatments for CF patients aim to maintain lung function by the removal of mucus secretions from the lungs and to unblock airways. Physiotherapy is an integral part of this treatment pathway with most CF patients undergoing 2-4 sessions per day in the home environment. Techniques such as chest percussion, vibrations and other physical manipulations are performed with the patient required to be in specific postures to facilitate mucus expulsion. Specific breathing techniques also play an important part in CF therapy. Controlled breathing with or without specific devices is also used to maintain lung function (Cystic Fibrosis Australia 2009b; Cystic Fibrosis Australia 2009a). Pharmaceutical treatment options may include the use of conventional nebulisers which use either compression or jet propulsion to deliver medication, however these devices have relatively poor antibiotic delivery efficiency (approximately 30%) (Traini & Young 2009). These nebulisers require a compressor which in turn requires either a mains-operated power supply of a large battery and are therefore relatively large, bulky and noisy in comparison to the vibrating membrane nebulisers (Lass et al 2006).

A new generation nebuliser, the I-neb Adaptive Aerosol Delivery System (Philips Respironics Ltd), also employs a vibrating mesh, with the added advantage of software which senses the patient's breathing patterns and pulses the aerosol only during inspiration (Dhand 2010).

SAFETY AND EFFECTIVENESS ISSUES

A recent published review did not identify any studies that compared the new vibrating membrane nebulisers to conventional compression nebulisers for the delivery of medication to CF patients. Although a large number of devices are available on the market, the FDA has taken the step to approve only the devices used with the drug combination that was used during clinical trials. That is, a device may be approved for use with tobramycin following a clinical trial, but further trials would need to be conducted for that device to be used with another antimicrobial such as aztreonam. This review also identified a lack of Phase III clinical trials comparing the clinical effectiveness of the delivery devices for the treatment of CF patients. This review identified the following two studies by Rottier et al (2009) and Hubert et al (2009) as the only two studies which described the use of the eFlow® Rapid nebuliser (Falagas et al 2010).

In the small cross over study by Hubert et al (2009) compared the delivery of a tobramycin (TOBI) solution for inhalation via the eFlow® Rapid nebuliser compared to the LC Plus™ nebuliser (level III-2 intervention evidence). CF patients ≥6 years (n=25) with chronic *Pseudomonas aeruginosa* infection were randomly assigned to receive TOBI (300mg, or 6o mg/ml) twice daily for 15 days either via the eFlow® Rapid or the LC Plus™ device. After a one week free from inhaled TOBI, but continuing on with standard therapy, the patients crossed-over and used the alternative device for 15 days. Only 22 patients could be included for pharmacokinetic evaluation on the basis of compliance criteria.

The mean nebulisation times were significantly shorter for the eFlow® Rapid compared to those obtained with the LC Plus™ on Day 1 (7.4 ± 1.7 vs 17.6 ± 4.0 mins, $p<0.0001$) and Day 15 (9.2 ± 5.1 vs 16.0 ± 2.8 mins, $p<0.001$). Patient compliance was high for both groups using both devices, ranging from 96.6 ± 6.4 per cent to 99.1 ± 2.1 per cent. Although shorter nebulisation times are associated with greater patient compliance over longer periods of time, this finding could not be confirmed due to the short study period. TOBI concentrations in patient sputum were measured and due to the large standard deviations, indicating great variation, no difference between the two devices could be identified. The maximum TOBI concentration on Days 1 and 15 for the eFlow® was 981 ± 1191 and 1575 ± 2182 µg/g, respectively, and were 754 ± 927 and 769 ± 823 for the LC Plus for Day 1 and 15, respectively. In addition, peak concentrations of TOBI in sputum were achieved in similar times by both devices, with a median of 0.5 hours. Although none of the measured pharmacokinetic variables showed a difference between the devices, the

number of patients and the short study period made it unlikely that this study had enough power to detect any differences.

Although no clinically significant bronchospasm event was reported during this study, 19 and 16 patients reported mild to moderate adverse events associated with the inhalation of TOBI with the eFlow® and the LC Plus™ device, respectively. Adverse events included headache, cough, dyspnoea and abdominal pain, however none were considered serious enough to discontinue treatment (Hubert et al 2009).

The performance of the Pari eFlow® Rapid nebuliser was assessed in a small observational study conducted by Rottier et al (2009) in the Netherlands (level IV intervention evidence). The effectiveness of the device in treating CF patients was not reported. Fifteen adult patients with CF who had been treated with tobramycin (TOBI) using the Pari LC Plus™ nebuliser plus Turboboy™ compressor were switched to using the eFlow® Rapid nebuliser to administer TOBI for six months (3 cycles of 28 days TOBI treatment). TOBI is widely regarded as the most effective antibiotic to treat *Pseudomonas aeruginosa* infection. Devices were then surrendered for assessment. A subgroup of eight of these patients repeated this testing protocol for a further six months after further instruction on the cleaning and care of the device. Of interest was patient care and maintenance of the device and its ability to then deliver the appropriate therapeutic dose of TOBI.

All patients indicated that they had maintained their eFlow® devices according to instructions, however the majority of devices were returned with polluted meshes. Further cleaning instructions were issued during series II in an attempt to alleviate this problem, however the majority of eFlow® devices in series II also were returned with polluted meshes, which would indicate that the timely replacement of the mesh is required to provide optimum drug delivery.

The parameters of drug delivered by the new and used eFlow® devices and the new and used LC Plus device are summarised in Table 1. The volume median diameter of TOBI delivered from a new eFlow® is significantly higher (24%) than that delivered by a new LC Plus (3.5 vs 2.8 µm, $p < 0.05$) but the relative span of the size distribution[1] was significantly narrower for the eFlow® (1.3 vs 2.2, $p < 0.05$). The total nebulisation time of the eFlow® increased significantly with device use with a time of 6.7 minutes for a new device compared to 8.7 minutes for a used one ($p<0.05$). It was also found that when the used eFlow® devices were tested three times each with three different ampoules (a total of 63 measurements) of medication that the device shut down prematurely before the end of nebulisation in 51 per cent of measurements. The error rate was greater for the eFlow® devices in series one (56%) than for series two (42%) indicating that further cleaning instructions presented to

[1] Span = (particle diameter at 90% cumulative size - particle diameter at 10% cumulative size) / particle diameter at 50% cumulative size. A small span indicates a narrow particle size distribution.

patients may have been of benefit. Early shut down of the device resulted in a reduced dosage of medication being delivered. Of a potential average TOBI dose of 5.3 grams, the used eFlow® devices delivered between 1.15 (22%) and 4.21 grams (79%), compared to new devices which delivered between 3.67 (69%) and 4.02 grams (76%). By replacing the polluted mesh in the used devices nebuliser times and drug delivery doses were normalised.

Table 1 Comparison of the parameters of delivered drug using new and used eFlow and LC Plus devices

Device	Volume median diameter in microns (X_{50}) (range)	Relative span of the size distribution $(X_{90} – X_{50})/X_{50}$	Delivered dose (gm drug solution) (range)	Total nebulisation time (min) (range)	Average output rate (g/min)
eFlow, new	3.5 (3.3 - 3.7)	1.3	3.85 (3.67 – 4.02)	6.7 (5.5 – 8.0)	0.58
eFlow, used Series 1	3.8 (3.3 - 4.3)	1.3	3.35 (1.65 – 4.21)	9.0 (5.5 – 10)	0.37
eFlow, used Series 2	3.5 (2.8 – 4.0)	1.3	3.48 (1.15 – 4.09)	8.7 (6.5 – 10)	0.40
LC Plus, new	2.8 (2.7 – 3.0)	2.2	3.44 (3.41 – 3.5)	6.9 (6.8 – 6.9)	0.50
LV Plus used	3.3 (2.8 – 4.2)	2.5	4.19 (3.61 – 4.44)	13.0 (8.0 – 20.5)	0.32

These results indicate that the eFlow® device delivers an aerosol which contains larger droplets of medication in a narrower size range (less variability) than the LC Plus, which should result in a greater proportion of the drug being deposited in the upper airways. Shorter nebulising times when using the eFlow® Rapid nebuliser should also result in greater patient compliance, however, no data were presented on the effectiveness of the two delivery devices in terms of patient symptoms. It is clear that patient compliance with cleaning practices is of importance to maintain therapeutic levels of drug delivery.

COST IMPACT

No cost-effectiveness studies reporting on the use of the eFlow® Rapid were identified. The Pari eFlow® Rapid costs approximately $1,740, compared to $440 for a conventional nebuliser. The majority of the cost is borne by the patient with some private health insurance companies covering part of the cost (personal communication Technipro-PulmoMed Pty Ltd).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

The use of the correct type of nebuliser and medication may prolong the life expectancy of patients with CF therefore it is critically important to identify which combination of device and medication is effective for each individual patient. Consideration may have to be given to enable equal access to all treatment devices regardless of cost.

OTHER ISSUES

There are at least 10 clinical trials currently underway or have recently been completed, all of which are more concerned with the effectiveness of the administration of pharmaceutical agents for the treatment of cystic fibrosis rather than the effectiveness of the Pari eFlow® nebuliser itself The following five studies have been completed: the randomised, crossover trial *Tobramycin Inhalation Solution Administered by eFlow Rapid Nebulizer: Scintigraphy Study* for patients with cystic fibrosis (n=12) (NCT ID: NCT00399945); the randomised, crossover trial *Tobramycin Administered by eFlow Rapid Nebulizer: Pharmacokinetic Study* for patients with cystic fibrosis (n=20) (NCT ID: NCT00420836); the crossover study *Pharmacokinetic Evaluation of an 8 -Week Treatment With Inhaled Tobramycin* for Pseudomonas Infections (n=50) (NCT ID: NCT00634192) completed August 2009, the randomised controlled trial *Safety, Pharmacokinetic and Pharmacodynamic Study of MP-376 in Patients With Cystic Fibrosis* (n=40) (NCT ID: NCT00503490) completed December 2007; and the cohort study (observational model) *Safety, Tolerability and Pharmacokinetics of MP-376 Administered for 14 Days to Stable Pediatric (CF) Patients* (n=27) (NCT ID: NCT00840333), completed December 2009. One randomised controlled study, *The Short Term Safety and Efficacy of Inhaled L-Arginine in Patients With Cystic Fibrosis*, was listed as recruiting, although it was stated that the completion date of the study was May 2009 (NCT ID: NCT00405665). Four studies were listed as active but not yet recruiting: the randomised controlled trial *MP-376 (Aeroquin™, Levofloxacin for Inhalation) in Patients With Cystic Fibrosis* (n=261) (NCT ID: NCT01180634) to be completed by May 2012; the randomised crossover trial Pharmacokinetic Study of Bramitob® Administered for Inhalation by Pari eFlow® vs Pari LC® PLUS Nebulizer for patients with cystic fibrosis (n=24) (NCT ID: NCT01116089) to be completed by February 2011; the randomised controlled trial *Aztreonam for Inhalation Solution (AZLI) vs Tobramycin Inhalation Solution (TOBI®) in Patients With Cystic Fibrosis & Pseudomonas Aeruginosa* (n=200) (NCT ID: NCT00757237) to be completed by November 2010; and the randomised controlled trial *Safety and Efficacy Study of Aztreonam for Inhalation Solution (AZLI) in Patients With Cystic Fibrosis and Chronic Burkholderia Species Infection* (n=100) (NCT ID: NCT01059565) which was registered to begin in February 2010 (US National Institutes of Health)

SUMMARY OF FINDINGS

There was a dearth of comparative evidence describing the use of the eFlow® nebuliser device for the treatment of cystic fibrosis patients. Both of the included studies reported shorter nebulisation times in comparison to conventional compressor nebulisers, which should translate into greater patient compliance and therefore improved therapeutic outcomes. However, this conclusion cannot be supported by the

evidence included for assessment in this summary. Studies with long-term endpoints are required to confirm this speculation.

Consideration should also be given to the large number of other nebulisation devices that are coming onto the market, including the eFlow®. In addition, the safety and effectiveness of the device needs to be considered when different pharmaceuticals are used.

HEALTHPACT ASSESSMENT:

Although only low level of evidence was available for inclusion in this assessment, the eFlow® device shows potential for improved therapeutic outcomes due to the associated shorter nebulisation times. Patient compliance with medication may play a role in the uptake of this technology. There are a number of clinical studies either recently completed or commenced which may provide more detailed information regarding the effectiveness of this device. HealthPACT will await further feedback from clinicians regarding the effectiveness and expected uptake of this device.

NUMBER OF INCLUDED STUDIES

Total number of studies	2
Level III-2 intervention evidence	1
Level IV intervention evidence	1

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SEARCH CRITERIA TO BE USED:

Administration, Inhalation
Anti-Bacterial Agents/administration & dosage/*pharmacokinetics
Cross-Over Studies
Cystic Fibrosis/*complications
Lung Diseases
Nebulizers and Vaporizers
Aerosols
Cystic Fibrosis/*drug therapy

HEALTH PACT DECISION:

☐ Horizon Scanning Report	☐ Full Health Technology Assessment
☐ Monitor	☐ Archive
☐ Refer	☐ Decision pending

PRIORITY RATING

☐ **High**	☐ **Medium**	☐ **Low**