CPAG Summary Report for Clinical Panel – 1621 Levofloxacin nebuliser solution for chronic pseudomonas lung infection in cystic fibrosis (Adults)

The Benefits of the Proposition – Nebulised levofloxacin compared to placebo to treat chronic pseudomonas lung infection in patients with cystic fibrosis			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [A]	In a study (Flume et al, 2016) of patients with cystic fibrosis who were treated with levofloxacin (n=220) or placebo (i.e. a dummy treatment) (n=110), 3.2% of patients who were treated with levofloxacin reported any treatment emergent serious adverse events compared to 0% in the placebo group. 1.8% of patients treated with levofloxacin had adverse events leading to withdrawal from study compared to 0.90% in the placebo group.

			Dysgeusia (taste disturbance) was the most common treatment-related adverse event, and this was reported in 35.2 % of the treatment group compared to 0% in the placebo group
11.	Delivery of intervention	Not measured	

Other health outcome measures determined by the evidence review - Nebulised levofloxacin compared to placebo to treat chronic pseudomonas lung infection in patients with cystic fibrosis			
No	Outcome measure	Grade of evidence	Summary from evidence review
1.	Time to exacerbation	Grade A	Cystic fibrosis is a lifelong progressive disease, primarily affecting lung function. Patients have periods where their lung function and symptoms are worse than usual (exacerbations). The primary endpoint of this study (Flume et al, 2016) was “time to exacerbation” i.e. the time from a patient starting this treatment or placebo to an exacerbation of lung disease. There is general agreement that a validated definition of exacerbation does not exist. In this study, exacerbation was defined as changes in at least four out of 12 respiratory signs or symptoms. In a study (Flume et al 2016) of patients who were treated with levofloxacin (n=220) or placebo (n=110), there was no statistically significant difference (i.e. a statistical test was applied to determine if any difference between the two treatments could have been due to chance alone) in time to protocol-defined pulmonary exacerbations between treatment arms (HR = 1.33, 95% CI 0.96–1.84).

			In other words, the difference in time to exacerbation between levofloxacin and placebo was small, and might have been due to chance alone; the primary endpoint in this study was not met. It is important to note that patients in this study received one treatment cycle only; it is usual for studies of this condition to take place over a longer period than this. The potential benefits resulting from this drug may have been underestimated because of the short duration of treatment. The choice of outcome measure in this study may also have had the effect of understating its true benefit.
2.	FEV1 (% predicted	Grade B	FEV1 (forced expiratory volume in one second) is the amount of air which a patient can expel in one second of forced expiration. This amount of air is reduced if the lungs are unable to expand fully and/or if there is an obstruction anywhere from the lungs to the mouth. Patients with a reduced FEV1 are more likely to have the sensation of finding it difficult to breathe, and are more likely to be breathless. FEV1 varies by age, height and gender, and thus the value for any given patient is usually expressed as a proportion of what would be expected (i.e. FEV1% predicted) for an average person of the same age, height and gender as the patient. In a study (Flume et al, 2016) of patients with cystic fibrosis who were treated with levofloxacin (n=220) or placebo (n=110), the difference between the treatment groups favoured the levofloxacin group, with an LS (least square) mean difference of 1.31 (95% CI 0.27, 2.34) i.e. FEV1 predicted

			increased in the group of patients treated with levofloxacin by 1.31% more, on average, than in the group of patients who received placebo. In this study, patients treated with levofloxacin showed a greater improvement in the amount of air that they were able to forcibly expire in one second than patients who were treated with placebo. It is important to note that patients in this study received one treatment cycle only; it is usual for studies of this condition to take place over a longer period than this. The potential benefits resulting from this drug may have been underestimated because of the short duration of treatment. The choice of outcome measure in this study may also have had the effect of understating its true benefit
3.	Sputum bacterial density	Grade B	Sputum density refers to the number of colonies of pseudomonas aeruginosa bacteria (i.e. a type of bacteria which causes infections, often found in the lungs of adult patients with cystic fibrosis and rarely found in the lungs of patients who do not have cystic fibrosis) which are grown in a given volume of sputum. A higher number indicates a greater level of infection. In this study (Flume et al, 2016) of patients with cystic fibrosis who were treated with levofloxacin (n=220) or placebo (n=110), the difference in change from baseline to day 28 between the treatment groups was an LS mean difference of − 0.63 log10 CFU/g sputum favouring the levofloxacin group (95% CI − 0.95) i.e. patients treated with levofloxacin had a lower number of pseudomonas aeruginosa colonies in their sputum,

			indicating a lower level of infection; the magnitude of this difference is such that it is unlikely to be due to chance alone. It is important to note that patients in this study received one treatment cycle only; it is usual for studies of this condition to take place over a longer period than this. The potential benefits resulting from this drug may have been underestimated because of the short duration of treatment. The choice of outcome measure in this study may also have had the effect of understating its true benefit.
4.	Respiratory domain of the cystic fibrosis questionnaire-revised (CFQ-R)	Grade A	The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a disease-specific health-related qualify of life measure for children, adolescents and adults with cystic fibrosis (CF). It measures a number of factors relevant to patients with this disease. It was developed through focus groups and interviews with CF patients and health care professionals, and is very widely used in research studies and in routine clinical practice. In this study (Flume et al, 2016) of patients with cystic fibrosis who were treated with levofloxacin (n=220) or placebo (n=110), there was no significant difference between nebulised levofloxacin and placebo: LS mean difference 0.28; 95% CI −2.30 to 2.85 i.e. there was no difference in this quality of life measure between patients who were treated with levofloxacin and those who were treated with placebo. It is important to note that patients in this study received one treatment cycle only; it is usual for studies of this condition to take place over a

			longer period than this. The potential benefits resulting from this drug may have been underestimated because of the short duration of treatment. The choice of outcome measure in this study may also have had the effect of understating its true benefit.

Other health metrics determined by the evidence review - Nebulised levofloxacin compared nebulised tobramycin to treat Chronic pseudomonas lung infection in cystic fibrosis			
No	Metric	Grade of evidence	Summary from evidence review
1	FEV_1 (% predicted)	Grade B	FEV1 (forced expiratory volume in one second) is the amount of air which a patient can expel in one second of forced expiration. This amount of air is reduced if the lungs are unable to expand fully and/or if there is an obstruction anywhere from the lungs to the mouth. Patients with a reduced FEV1 are more likely to have the sensation of finding it difficult to breathe, and are more likely to be breathless. FEV1 varies by age, height and gender, and thus the value for any given patient is usually expressed as a proportion of what would be expected (i.e. FEV1% predicted) for an average person of the same age, height and gender as the patient. In this study (Elborn et al, 2015) of patients with cystic fibrosis who were treated with levofloxacin (n=189) or tobramycin (n=93), the least squares (LS) mean between-group difference (levofloxacin minus tobramycin) in FEV_1 was 1.86% [95% CI − 0.66 to 4.39%] i.e. levofloxacin was slightly better than tobramycin at improving FEV1 predicted, but this difference was small and could have been due to chance alone. This was an open-label study i.e. all patients knew which drug they were

			receiving. It is desirable in randomised studies if neither the patient nor the researcher knows which drug the patient was receiving. This was not possible in this study due to the different design of nebulisers that were used for each drug. Being an open-label study may have influenced patient care and the assessment of subjective outcomes (e.g. quality of life). In addition, patients had already had a substantial period of treatment with tobramycin prior to the study. It is difficult to know whether this affected the outcomes of this study. This could favour the levofloxacin group, if the response to tobramycin diminishes over time; or it could favour the tobramycin group as we might expect fewer discontinuations in a group of patients who had already been treated with this drug.
2	Mean time to first exacerbation (days)	Grade B	Cystic fibrosis is a lifelong progressive disease, primarily affecting lung function. Patients have periods (exacerbations) where their symptoms and lung function are worse than usual, and sometimes they never fully recover to baseline. More exacerbations result in worse quality of life and earlier death. The primary endpoint of this study (Elborn et al, 2015) was the time from a patient starting this treatment or placebo to an exacerbation of lung disease. There is general agreement that a validated definition of exacerbation does not exist. In this study, exacerbation was defined as changes in at least four out of 12 respiratory signs or symptoms. In this study of patients who were treated with levofloxacin inhaled solution (LIS) (n=189) or tobramycin

			inhaled solution (TIS) (n=93), the time to first exacerbation was not significantly different in the LIS group (median 131 days) compared to the TIS group (median 90.5 days) (HR = 0.78; 95% CI: 0.57 to 1.07, p = 0.15 i.e. although the average time to first exacerbation was longer in patients treated with levofloxacin than in patients treated with tobramycin, this difference was relatively small and may have been due to chance alone. This was an open-label study ie all patients knew which drug they were receiving. It is desirable in randomised studies if neither the patient nor the researcher knows which drug the patient was receiving. This was not possible in this study due to the different design of nebulisers that were used for each drug. Being an open-label study may have influenced patient care and the assessment of subjective outcomes (e.g. quality of life). In addition, patients had already had a substantial period of treatment with tobramycin prior to the study. It is difficult to know whether this affected the outcomes of this study. This could favour the levofloxacin group, if the response to tobramycin diminishes over time; or it could favour the tobramycin group as we might expect fewer discontinuations in a group of patients who had already been treated with this drug.
3	Median time to administration of antipseudomonal antibiotics other than the study drug (days)	Grade B	There are a number of antibiotics used in the treatment of pseudomonas aeruginosa, and patients with cystic fibrosis are prone to a number of other infections as well. It is therefore standard practice in any study of antibiotics in patients with cystic fibrosis to assess whether

			antibiotics other than those in the study were required on clinical grounds. In this study (Elborn et al, 2015) of patients with cystic fibrosis who were treated with levofloxacin (n=189) or tobramycin (n=93), the median time to administration of antibiotics (excluding those drugs in the study) was 141 days for LIS and 110 days for TIS (HR = 0.73; 95% CI: 0.53 to 1.01; p = 0.04) i.e. patients who were treated with levofloxacin were less likely to require treatment with antibiotics other than those in the study, than were those patients who were treated with tobramycin, and this difference is unlikely to be due to chance. This was an open-label study ie all patients knew which drug they were receiving. It is desirable in randomised studies if neither the patient nor the researcher knows which drug the patient was receiving. This was not possible in this study due to the different design of nebulisers that were used for each drug. Being an open-label study may have influenced patient care and the assessment of subjective outcomes (e.g. quality of life). In addition, patients had already had a substantial period of treatment with tobramycin prior to the study. It is difficult to know whether this affected the outcomes of this study. This could favour the levofloxacin group, if the response to tobramycin diminishes over time; or it could favour the tobramycin group as we might expect fewer discontinuations in a group of patients who had already been treated with this drug.
4	Respiratory domain of the	Grade B	The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a disease-

	cystic fibrosis questionnaire-revised (CFQ-R)		specific health-related qualify of life measure for children, adolescents and adults with cystic fibrosis (CF). It measures a number of factors relevant to patients with this disease. It was developed through focus groups and interviews with CF patients and health care professionals, and is very widely used in research studies and in routine clinical practice. In this study (Elborn et al, 2015) of patients with cystic fibrosis who were treated with levofloxacin (n=189) or tobramycin (n=93), scores in the respiratory domain of the CFQ-R were similar at baseline. The LS means increased (i.e. improvement) in the LIS group and decreased in the TIS group at day 28 (difference of 3.19 units, p = 0.05. The results were similar between the two groups at the end of the study (i.e. after three doses.) In other words, any difference in patient perception of their lung function between the two antibiotics was small, and may have been due to chance alone. This was an open-label study ie all patients knew which drug they were receiving. It is desirable in randomised studies if neither the patient nor the researcher knows which drug the patient was receiving. This was not possible in this study due to the different design of nebulisers that were used for each drug. Being an open-label study may have influenced patient care and the assessment of subjective outcomes (e.g. quality of life). In addition, patients had already had a substantial period of treatment with tobramycin prior to the study. It is difficult to know whether this affected

			the outcomes of this study. This could favour the levofloxacin group, if the response to tobramycin diminishes over time; or it could favour the tobramycin group as we might expect fewer discontinuations in a group of patients who had already been treated with this drug.
5	Sputum *P. aeruginosa* density	Grade B	Sputum density refers to the number of colonies of pseudomonas aeruginosa bacteria which are grown in a given volume of sputum. A higher number indicates a greater level of infection. In this study (Elborn et al, 2015) of patients with cystic fibrosis who were treated with levofloxacin (n=189) or tobramycin (n=93), both treatments reduced sputum *P. aeruginosa* density, with the magnitude of reduction being greater for TIS than LIS, although the difference in change from baseline to day 28 was not significantly different (LS mean difference 0.44 $\log_{10}$ CFU/g; 95% CI − 0.01 to 0.88) i.e. the difference between the two antibiotics was small, and might have been due to chance alone. This was an open-label study i.e. all patients knew which drug they were receiving. It is desirable in randomised studies if neither the patient nor the researcher knows which drug the patient was receiving. This was not possible in this study due to the different design of nebulisers that were used for each drug. Being an open-label study may have influenced patient care and the assessment of subjective outcomes (e.g. quality of life). In addition, patients had already had a substantial period of treatment with tobramycin prior to the study. It is

			difficult to know whether this affected the outcomes of this study. This could favour the levofloxacin group, if the response to tobramycin diminishes over time; or it could favour the tobramycin group as we might expect fewer discontinuations in a group of patients who had already been treated with this drug.