

APPENDIX V**CLINICAL TRIAL INFORMATION LEAFLET 1 (FOR ADULTS)**
Version 001; Dated 01/11/02

A randomised, open label study to compare the safety of a dry powder formulation of inhaled Colomycin (colistimethate sodium) and nebulised Colomycin in cystic fibrosis patients with *Pseudomonas aeruginosa* lung infection

PROTOCOL NO: COLO/DPI/02/05**Why have I received this leaflet?**

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to discuss it with someone if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not to take part.

What is the purpose of the study?

Colistimethate sodium (Colomycin) is an antibiotic medicine that has been marketed in the UK for over 40 years. It is used nowadays for the treatment of *Pseudomonas aeruginosa* chest infections in cystic fibrosis. At the moment, patients can either inhale Colomycin through a nebuliser, or be given Colomycin by injection. Previously, treatment with inhaled Colomycin was given in hospital but now is more commonly given at home. Most cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection will be receiving the nebulised form of the medicine, either alone or with another antibiotic.

The company that makes Colomycin has developed a new way for patients to inhale the medicine. The Colomycin can now be inhaled as a powder (contained in capsules) which is sucked in through a pocket-sized, hand held device. Colomycin powder is made of the same active ingredient as standard Colomycin, but has been made into a much finer powder so that you can use it in a special inhaler device.

We believe that using the Colomycin powder in the pocket-sized device will be easier and more convenient for patients. Colomycin by nebuliser, is, as you know, time consuming. This new treatment will take less time to prepare and to breathe in and less time will be spent cleaning equipment after use. We hope that the advantages of this new treatment will lead to a better quality of life for cystic fibrosis patients.

We have already given dry powder Colomycin to 12 healthy people and 22 patients with cystic fibrosis at a single dose of 125 mg (1 capsule). No serious side effects were reported, although mild side effects such as cough, throat irritation and unpleasant taste were found. We are doing this study because we would like to see whether giving dry powder at a dose of 1 capsule (125 mg), twice a day, every day for 4 weeks is just as safe as nebulised Colomycin.

Why have I been chosen?

You are a cystic fibrosis patient who is currently suffering from a lung infection with bacteria called *Pseudomonas aeruginosa*. If you agree to take part, you will be one of about 12-16 patients taking



part in the study.

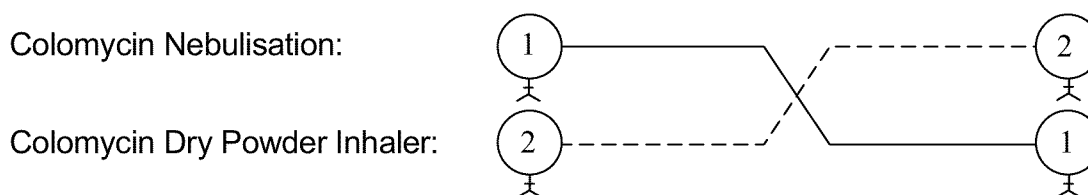
Do I have to take part?

NO. Entry into the study is entirely voluntary. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time and you would not have to give a reason. If you decide not to take part or if you withdraw at any time, the standard of medical care that you receive either now or in the future will not be affected. Your doctor is also able to withdraw you from the trial at any point if they feel there is good reason (e.g. if it is in your interests to do so).

What will happen if I take part?

Sometimes, because we do not know which way of treating patients is best, we need to make comparisons. People are randomly put into groups and then the results are compared. The groups are selected by a computer which has no information about the individual i.e. by chance. (This process is called randomisation).

This study has been designed to be a 'cross-over' study. It is called this because during the course of the study, you will first be given Colomycin by one route of delivery (by dry powder inhalation or by nebulisation) and afterwards you will be given Colomycin by the other route of delivery. Hence, you may receive treatment in the order of patient 1 below or in the order of patient 2 below:-



On starting the trial, you will be entered into one of two groups of patients by randomisation.

1. One group of patients will first be given
 - a) Colomycin 2 million units (2 mega units) twice a day for 4 weeks, by the usual route of nebulisation (this may be a different dose to the one you may have had before), and afterwards, will receive
 - b) Colomycin 125 mg twice a day for 4 weeks by the new dry powder inhalation device
2. The other group of patients will first be given
 - a) Colomycin by the new dry powder inhalation device, and afterwards, will receive
 - b) Colomycin by nebulisation

The study has been designed so that there will be an equal number of patients in each group. Therefore, you have an equal chance to receive treatment in the order of patient 1 above or in the order of patient 2 above.

This trial is an open label trial, which means that you and your doctor will know which treatment group you are in. It is important that you answer any questions as honestly as possible for the trial



to work.

The study will last for about 9 weeks. You will be taking trial medication twice a day, every day for 2 periods of 4 weeks (8 weeks total). The additional study time is needed because before each treatment period you will be asked not to take any Colomycin (or any other antibiotics used to treat *Pseudomonas aeruginosa* infections) for a short time (minimum of 72 hours) so that we can make a fair comparison between the two different ways of delivering Colomycin.

Will I have to alter my lifestyle to take part?

The study has been designed so that you will experience the minimum amount of additional discomfort and inconvenience. However, the nature of a clinical trial does mean that some changes will be necessary.

1. Clinic visits You will be required to attend the clinic on six occasions so that the doctor can:
 - Check your health.
 - Perform lung function tests to see how well your treatment is working.
 - At four of these visits (beginning and end of each treatment period) we would also like to collect a blood sample and a urine sample so that we can monitor your general health and also as a safety procedure for checking the levels of drug in your body.
2. Taking the trial medication Probably the biggest change in your everyday routine is that you will be asked to take the trial medication twice a day every day for 8 weeks.
3. Completing a diary card You will be asked to complete a patient diary card during the study (you may like to ask to see what this looks like before agreeing to take part in the trial).
4. Completing a questionnaire You will also be asked to complete a questionnaire about your health at four visits (at the screening visit (today), at the beginning and end of the first treatment period, and at the end of the second treatment period). Again you may like to ask to see what this looks like.
5. Changes to usual treatment As mentioned above, you will be asked to stop taking Colomycin (or other antibiotics used to treat *Pseudomonas aeruginosa* infections) for a short period (minimum of 72 hours) before starting each of the 4 week treatment periods.

What are the alternatives for diagnosis or treatment?

There are other antibiotic treatments that are currently used in the treatment of lung infection with *Pseudomonas aeruginosa*. However, there is currently no other antibiotic that can be inhaled as a dry powder and it is hoped that this new Colomycin dry powder will be the easiest and most convenient way for patients to receive their antibiotic treatment. Using antibiotics other than Colomycin increases the risk that the bacteria causing the infection will develop resistance to the antibiotic (i.e. surviving despite antibiotic use). Colomycin is somewhat different from other antibiotics in the way in which it 'attacks' bacteria and over the 40 years that Colomycin has been used, resistance levels remain extremely low.

Are there any side effects or disadvantages of taking part?

No major side effects have been reported with nebulised Colomycin, and the medicine appears to be safe and tolerable. However, there is the possibility of some side effects, such as coughing and chest tightness with inhaled Colomycin. If you experience side effects like these after taking your trial medication, you can take 1-2 puffs on your salbutamol inhaler. If you need to take more than 4 puffs of salbutamol within 1 hour of taking trial medication, you should contact your doctor. Your



doctor will then decide whether you should carry on taking trial medication, or whether you should be withdrawn from the study.

When Colomycin has been given by injection, there is the possibility of side effects such as dizziness, pins and needles or numbness. However, on the basis of about 15 years use of nebulised Colomycin, it is extremely unlikely that you will experience these injection related side effects during this trial as we do not expect there to be much absorption of Colomycin from the lungs to the bloodstream.

You will be monitored very closely for any signs of side effects.

Are there any benefits of taking part?

Whilst you are receiving the Colomycin dry powder inhaled treatment you may find that taking the antibiotic in this way is less of a 'burden' to you. If the study proves successful, it may benefit other cystic fibrosis patients in the future, allowing patients to enjoy the increase in freedom which this new type of treatment may provide.

What if something goes wrong?

In the unlikely event of something going wrong, this study is covered by the sponsoring company's clinical trials insurance. In addition, the nebulised trial medication is a licensed product and is therefore covered by product liability insurance. If you should suffer injury as a result of participating in this study, the Sponsor agrees to operate in good faith by the 'Clinical Trial Compensation Guidelines' published in 1991 by the Association of the British Pharmaceutical Industry (ABPI) guidelines.

Broadly speaking, the ABPI guidelines recommend that 'the sponsor', without legal commitment, should compensate you without you having to prove that it is at fault. This applies in cases where it is likely that such injury results from giving any new drug or any other procedure carried out in accordance with the protocol for the study. The sponsor will not compensate you where such injury results from any procedure carried out which is not in accordance with the protocol for the study.

Indemnity will not cover negligence on the part of the staff performing the study. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

Will taking part be kept confidential?

We know that you would want your medical records to be kept confidential. During the study it may be necessary for certain officials (e.g. the sponsor, Government Regulatory Authorities or the Hospital Ethics Committee) to look at your medical notes for purposes of analysing the results and to check that the study is being carried out correctly. All information which is collected about you during the course of research will have your name and address removed so that you cannot be recognised from it.



What will happen to the results of the study?

The results of the study will be looked at closely by a Safety Monitoring Committee who will decide whether the dose you have been given is appropriately tolerable. If the committee approve, we hope to do a further study with a much larger number of patients to show that delivering Colomycin by dry powder inhalation is just as good as or better than existing medication in maintaining lung function. Eventually, we hope to obtain approval to make this new product available to all cystic fibrosis patients so that they will benefit from taking their antibiotic treatment in this anticipated more convenient way. You will not be identified in any way in any report or publication.

Who is organising and funding the research?

Your doctors will **not** profit from including you in this study.

The sponsor company funding this project is Forest Laboratories UK Limited; this company sells Colomycin and has designed and organised this study.

Who has reviewed the study?

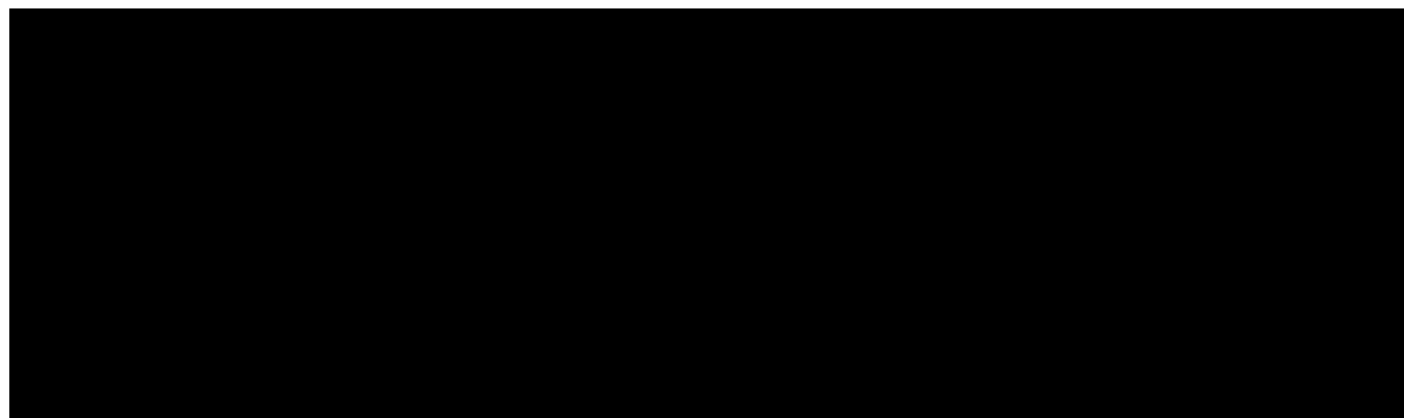
The study has been reviewed and approved by the Medicines Control Agency and has been approved by the _____ LREC.

Who can I contact for further information?

Your doctor taking clinical responsibility for you in the study.



If you agree to take part in this study, you will receive a copy of the information sheet to keep and a signed copy of the consent form.

Thank you once again for reading this information

APPENDIX VI
CONSENT FORM 1 (For Adults)
 Version 001; Dated 01/11/02

**A RANDOMISED, OPEN LABEL STUDY TO COMPARE THE SAFETY OF A DRY POWDER
 FORMULATION OF INHALED COLISTIMETHATE SODIUM AND NEBULISED
 COLISTIMETHATE SODIUM IN CYSTIC FIBROSIS PATIENTS INFECTED WITH
 PSEUDOMONAS AERUGINOSA.**

PROTOCOL NO: COLO/DPI/02/05

Patient Number

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Patient Initials

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Parts A, B & C MUST be completed before the patient is entered into the study

PART A

Please tick
YES **NO**

1. Have you read the clinical trial information leaflet provided? ☐ ☐
2. Has the nature and purpose of the study been explained to you? ☐ ☐
3. Have you had the opportunity to ask questions and discuss the study? ☐ ☐
4. Have you received satisfactory answers to your questions? ☐ ☐
5. Have you received enough information about the study? ☐ ☐
6. Have you had adequate time in which to decide whether to participate?
in the study? ☐ ☐
7. Who has spoken to you about the study? Prof./Dr/Mr./Mrs./Ms _____

PART B

Please tick
YES **NO**

1. Do you understand that participation in the study is voluntary and that you are free to withdraw at any time (you do not have to give a reason for withdrawing and it will not affect your future medical care)? ☐ ☐
2. We know that you would want your medical records to be kept confidential. However, during the study it will be necessary for certain officials (i.e. the sponsor, Government Regulatory Authorities or the Hospital Ethics Committee) to look at your medical notes (these people understand the need for confidentiality). In addition to this, do you authorise your doctor to contact your GP to make known your participation in this study and to disclose details of your relevant medical and drug history, in confidence? ☐ ☐
3. Do you understand that if you should suffer injury as a result of participating in this study the sponsor agrees to operate in good faith by the "Clinical Trial Compensation Guidelines" published in 1991 by the Association of the British Pharmaceutical Industry? ☐ ☐

PART C

PATIENT: I _____ **hereby consent to take part in the above-titled study, the nature and purpose of which I understand.**
 (Patient's full name – in their own handwriting)

Signed: _____ **Date:** _____
 (Patient's signature)

INVESTIGATOR: I hereby declare that I have discussed the above-titled study in accordance with GCP Guidelines. The patient has understood all the information he/she has been given and freely chooses to participate in this study.

Signed: _____ **Date:** _____
 (Investigator's Signature)



Protocol Number: COLO/DPI/02/05

Final Version 01 November 2002

CONSENT FORM 2**Agreement from person with parental responsibility for a child to investigation or treatment for a child or young person**

Version 001; Dated 01/11/02

A RANDOMISED, OPEN LABEL STUDY TO COMPARE THE SAFETY OF A DRY POWDER FORMULATION OF INHALED COLISTIMETHATE SODIUM AND NEBULISED COLISTIMETHATE SODIUM IN CYSTIC FIBROSIS PATIENTS WITH LUNG INFECTION**PROTOCOL NUMBER: COLO/DPI/02/05**Patient number: Patient Initials: **Parts A, B, C, D & E MUST be completed before the patient is entered into the study****PART A**Please tick
YES NO

- | | | |
|---|--------------------------|--------------------------|
| 1. Have you and your child read the patient information leaflets provided? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Has the nature and purpose of the study been explained to you and your child? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Have you and your child had the chance to ask questions and discuss the study? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Have you and your child received satisfactory answers to your questions? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Have you received enough information about the study? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Have you had adequate time in which to decide whether your child should participate in this trial? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Who has spoken to you about the trial? _____ | | |

PART BPlease tick
YES NO

- | | | |
|---|--------------------------|--------------------------|
| 1. Do you understand that participation in the study is voluntary and that your child is free to withdraw at any time (you/ your child do not have to give a reason for withdrawing and it will not affect future medical care)? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. We know that you would want your child's medical records to be kept confidential. However, during the study it will be necessary for certain officials (i.e. the sponsor, Government Regulatory Authorities or the Hospital Ethics Committee) to look at your child's medical notes (these people understand the need for confidentiality). In addition to this, do you authorise the doctor to contact your GP to make known your participation in this study and to disclose details of your relevant medical and drug history, in confidence? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Do you understand that if your child should suffer injury as a result of participating in this study the sponsor agrees to operate in good faith by the "Clinical Trial Compensation Guidelines" published in 1991 by the Association of the British Pharmaceutical Industry? | <input type="checkbox"/> | <input type="checkbox"/> |



PART C**STATEMENT OF PARENT**

I agree to the participation of my child in this study as described in the patient information leaflet dated version and **I confirm** that I have 'parental responsibility' for this child.

Signature Date

Name (PRINT) Relationship to child

PART D**CHILD'S/ YOUNG PERSON'S AGREEMENT TO TREATMENT**

	Please tick	
	YES	NO
Have you read and understood the information given to you about taking part in this study?	<input type="checkbox"/>	<input type="checkbox"/>
Have you had the chance to ask questions?	<input type="checkbox"/>	<input type="checkbox"/>
Has somebody answered all your questions?	<input type="checkbox"/>	<input type="checkbox"/>
Do you have any other questions you would like to ask?	<input type="checkbox"/>	<input type="checkbox"/>

I agree to have the treatment I have been told about.

Name Signature

Date

PART E**PERSON WHO CONDUCTED INFORMED CONSENT DISCUSSION**

I hereby declare that I have discussed the above-titled study in accordance with GCP guidelines. The patient and his/ her parents have understood all the information they have been given. I have confirmed that they have no further questions and they have freely chosen for the child/ young person to participate in this study.

Signature Date

Name (PRINT) Position

