AZTEC-CF

Aztreonam for Inhalation Solution (AZLI) for the Treatment of Exacerbations of Cystic Fibrosis. An Open-label, Randomised Crossover Pilot Study of AZLI Plus Intravenous Colistin versus Standard Dual Intravenous Therapy.

Chief Investigator: **Dr Freddy Frost**
Sponsor: **Liverpool Heart and Chest Hospital NHS Foundation Trust**

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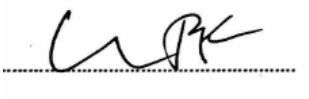
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: 

Name: Dr Freddy Frost

Date: 22/09/2016

Signed on behalf of the sponsor:

Signature 

Name: Gill Hamblin

Date: 26/09/2016

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TRIAL SUMMARY

Trial Title	Aztreonam for inhalation solution (AZLI) for the treatment of exacerbations of Cystic Fibrosis. An open-label, randomised, crossover pilot study of AZLI plus intravenous colistin versus standard dual intravenous therapy.	
Internal ref. no. (or short title)	AZTEC-CF	
Clinical Phase	Phase IV	
Trial Design	Open-label, randomised, cross-over study	
Trial Participants	Adults with cystic fibrosis	
Planned Sample Size	16	
Treatment duration	Two treatment arms of 14 days each	
Follow up duration	Up to 12 months	
Planned Trial Period	December 2016 – June 2018	
Test Investigational Medicinal Product(s)	Aztreonam for Inhalation Solution (AZLI) [Cayston®, Gilead Sciences Ltd]	
Formulation, Dose, Route of Administration	75mg TDS via inhalation (eFlow® PARI nebuliser)	
	Objectives	**Outcome Measures**
Primary	Are there immediate clinical benefits in using Cayston® plus an IV antibiotic as compared to two standard IV antibiotics	Average actual change from Day 1 (start of exacerbation) in % predicted forced expiratory volume in 1 second ($ppFEV_1$) at 7 days, the end of each arm of study (day 14
Secondary	Are there sustained clinical benefits in using Cayston® plus an IV antibiotic as compared to two standard IV antibiotics?	Time to first protocol-defined pulmonary exacerbation (or end point of 12 months if no subsequent exacerbation).
	Are there any quality of life benefits in using Cayston® plus an IV antibiotic as compared to two standard IV antibiotics?	Average change in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptom Scale (RSS) score.
	What effect does Cayston® have on the microbiome of patients with CF in the treatment of acute pulmonary exacerbations of CF?	PA sputum counts, total bacterial load and 16S microbiome Prevalence of resistance to antibiotics and changes in antimicrobial resistance (AMR)

FUNDER	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Gilead Sciences Gilead Sciences Europe Ltd North Building 2 Roundabout Avenue Stockley Park Uxbridge UB11 1AF Contact: colin.molokwu@gilead.com	Funding £114,018.60

ROLE OF STUDY SPONSOR AND FUNDER

AZTEC-CF is sponsored by Liverpool Heart and Chest Hospital NHS Foundation Trust (LHCH) and funded by Gilead Sciences, UK. Sponsor and Funder have internally reviewed the protocol but have not had any role in trial concept, design or development of the protocol and they will have no role in data analysis, interpretation or writing of results. The AZTEC-CF team control decisions regarding all of the above aspects. With regard to dissemination of results, the AZTEC-CF team will retain control of the data and results generated from this study and will disseminate the information to relevant meetings and peer-reviewed journals without influence from sponsor or funder.

KEY WORDS:

Cystic fibrosis

Inhaled antibiotics

Microbiome

Acute exacerbations

Infection

Aztreonam for inhalation (AZLI)

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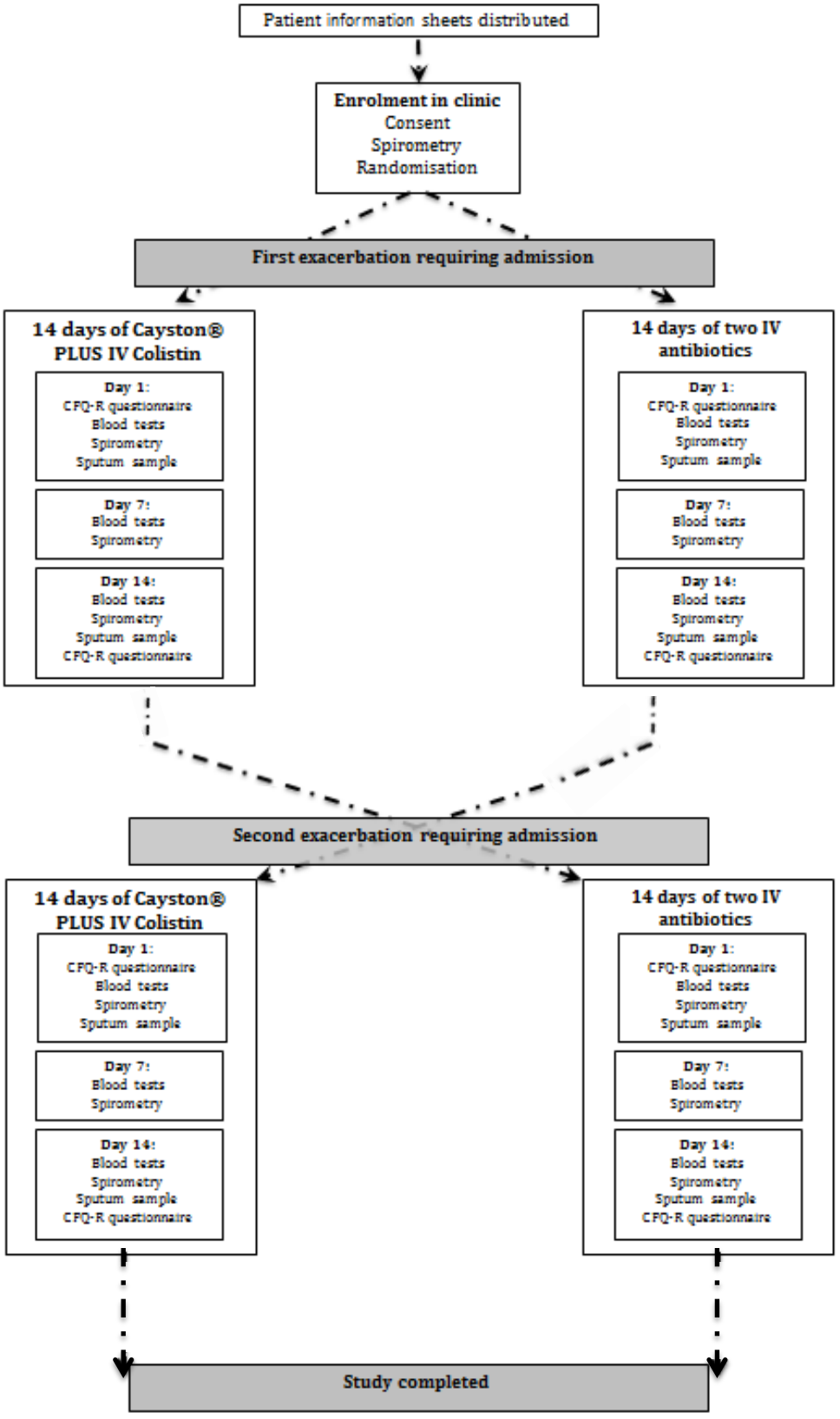
LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AMR	Antimicrobial resistance
AR	Adverse Reaction
AZLI	Aztreonam for Inhalation Solution
CA	Competent Authority
CF	Cystic fibrosis
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FEV1	Forced expiratory volume in 1 second
ppFEV1	Forced expiratory volume in 1 second (% predicted)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LHCH Trust	Liverpool Heart & Chest Hospital NHS Foundation
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NGS	Next Generation Sequencing
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PA	Pseudomonas aeruginosa
PI	Principal Investigator
PIC	Participant Identification Centre

PIS	Participant Information Sheet
QA	Quality Assurance
QIIME	Quantitative insights into microbial ecology
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

TRIAL FLOW CHART



STUDY PROTOCOL:

Aztreonam for inhalation solution (AZLI) for the treatment of exacerbations of Cystic Fibrosis. An open-label, randomised, cross-over pilot study of AZLI plus intravenous Colistin versus standard dual intravenous therapy.

1 BACKGROUND

Cystic Fibrosis (CF) is the UK's most common life-threatening inherited disease affecting over 10000 people. There have been significant improvements in CF survival since the 1930s when 70% of those with CF died in infancy, to a median predicted survival in 2013 of 43.5 years [1]. Early CF deaths are now rare: >95% of children with CF enter adulthood and those born in this century can expect to survive into at least their 6^{th} decade. Recent predictions are that the number of CF adults will increase by 78%, a finding that mostly results from the transition of children to adults, whereas the number of CF children will show a 20% increase [2]. The present population forecasts and projections are useful for planning paediatric and adult CF care.

This improving survival in CF has brought new complications and a number of co-morbidities such as CF related diabetes, CF related bone disease, issues around nutrition and segregation are now more prevalent, either as previously unexpected manifestations of the CF condition, or as a consequence of a lifetime of necessarily aggressive treatment regimens e.g. ototoxicity and nephrotoxicity. These improvements in survival are attributed to enhancements in screening, nutrition, drugs, paediatric and adult care, socio-economic factors and psycho-social support.

The genetic defect in CF, an autosomal-recessive defect, causes abnormal salt and water movements across mucus-producing cell surfaces resulting in thick mucus and end-organ damage, most apparent in the lungs and pancreas, but affecting most organs. This chronic airway inflammation leads to chronic infection with difficult to treat pathogens, the most significant of which is *Pseudomonas aeruginosa* (PA). Chronic airway infection is associated with progressive loss of lung function, which is the primary cause of death for CF patients [3]. PA has innate resistance to many antibiotics, and furthermore it can elude the host immune system and the action of antibiotics by forming free-floating biofilm-like aggregates [4]. The mainstay of CF treatment remains adequate antibiotic therapy that is effective against PA. In adults with chronic PA infection, pulmonary exacerbations are usually not caused by a new strain [5] and laboratory susceptibility might not always correlate with clinical response [6]. There is a concern that the use of a single antibiotic may be associated with increased levels of antibiotic resistance in PA [7, 8]. Hence it is common practice to choose two antibiotics with differing mechanisms of action, such as a beta-lactam and an aminoglycoside or polymixin to treat CF exacerbations.

It is a frequent clinical observation that patients with CF may improve clinically, even when PA present in their sputum is not fully sensitive to the antibiotics they have received. PA may show resistance to a single antibiotic in-vitro but a combination of two or more antibiotics may kill the organism. It has been shown that there is no relationship between the susceptibility of PA to ceftazidime and tobramycin, on a sample taken prior to an exacerbation and improvement in FEV_1 [6]. Moreover, patients often prefer an antibiotic combination that they have received previously, with good symptomatic improvement.

Upon exacerbation, antibiotics are routinely used intravenously (IV) and although they have improved survival by reducing sputum bacterial load and maintaining pulmonary function, they interfere with daily living and increase the risk of antibiotic hypersensitivity reactions and adverse drug effects [9]. Moreover, the complications associated with such use – nephrotoxicity and ototoxicity with aminoglycosides [10-12] and vascular access problems [13] are well known.

Nebulised versions of drugs which have excellent lung deposition, with higher sputum levels than the IV preparation and a low systemic bio-availability, are now available for prophylactic

suppression of chronic PA infection in these patients. The high endobronchial and sputum drug concentrations may render the traditional laboratory breakpoints meaningless.

There is now evidence that High Dose Nebulised Tobramycin (HDNT) is effective in the treatment of exacerbations associated with multi-resistant PA [14]. Importantly, HDNT has been shown to be safe, well tolerated with immediate renal sparing properties and a longer exacerbation free period compared to the IV preparation. This is important because each acute pulmonary exacerbation has a negative impact on 5-year survival equal to subtracting the equivalent of 12% FEV_1 [15] and has a profound negative impact on health related quality of life [16]. Moreover, there are significant costs associated with the requirement for IV therapy at home or in hospital; strategies such as nebulised antibiotics in acute pulmonary exacerbations might benefit patient time and quality of life as well as overall costs, resources and patient time.

2 RATIONALE

New approaches to antibiotic therapy in acute CF pulmonary exacerbations are needed and non-aminoglycoside medications such as Aztreonam Lysine Solution for Inhalation (AZLI), marketed as Cayston® (Gilead Sciences Ltd., UK) are now available for chronic use in PA infection in CF patients [17, 18]. Alternate-month, suppressive therapy with inhaled antibiotics is the standard of care for CF patients chronically colonised with PA [19, 20]. Current standard of care for acute exacerbations is treatment with two IV anti-pseudomonal antibiotics, one of which is usually an aminoglycoside. Intravenous antibiotics can cause systemic side-effects and end-organ damage, particularly when associated with long courses and frequent exposures as seen in CF. Inhaled antibiotics generally have much lower systemic absorption but still act at the intended site of action in the lung. Hence, they are an attractive avenue for new approaches to treating acute exacerbations; indeed a recent consensus statement from the CF Foundation has recommended their use for the treatment of acute exacerbations in some circumstances [21]. In its use as chronic suppressor therapy Cayston has demonstrated significant improvements in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) - Respiratory Symptoms Scale (RSS), time-to-need for IV or additional inhaled anti-pseudomonal antibiotics, FEV_1 and $\log_{10}$ PA colony forming units (CFUs) in sputum. The systemic absorption of Cayston® is very low (approximately 1% of the 500mg dose of IV aztreonam), making it an attractive candidate for acute use, however its effectiveness in acute exacerbations has not been studied.

To investigate this further we will use a randomised crossover trial design to carry out a pilot study comparing Cayston® with standard IV therapy on lung function in acute PA exacerbations in patients with CF.

The abundance of conventional CF pathogens such as PA does not always correlate with disease in all patients [22]. Recently it has become apparent that the lower airways in patients with CF are colonized by a more complex polymicrobial community referred to as the ‘microbiome’ [23-25], hence, the host response in CF is complicated and current conventional CF microbiological approaches give us only an incomplete picture. For example, there may be overlooked potential pathogens or other members of the microbial community that can influence known pathogens by acting as synergens, driving disease in many patients even where there is no obvious change in the dynamics of conventional CF pathogens. The upper airways, in particular the oral cavity, represent the most diverse microbiome site in the body [26, 27] and likely contribute to the CF lung microbiome.

The complexity of CF microbiome is not apparent using conventional clinical microbiology due to the fact some members of the microbiome are not readily cultured. For example, there are many anaerobes present in the CF lung, but anaerobic culture is not routinely carried out. Hence, assessments and microbial characterization of these complex microbial communities require the use of mostly culture independent methods. The bacterial gene encoding the small

ribosomal subunit 16S rRNA gene is widely used to define the composition of microbial communities [28]. The availability and reduced costs of next generation sequencing now enables amplified, variable regions of the 16S rRNA gene to be deep sequenced in order to determine the microbial population present, also known as the "16S Microbiome". These variable regions are unique to particular types of bacteria and therefore allow us to identify which bacteria are present in each sample. By evaluating the total bacterial population using 16S sequencing, a much better measure of the effects of antibiotics on the microbial community is obtained. 16S microbiomes are the new gold standard for looking at microbes in complex communities. Analyses using this approach have demonstrated subtle relationships between, for example, the "richness" (variety of species present) of a microbial population and lung function (i.e. low species richness is associated with decreased lung function) [23]. This will also help us to integrate airway microbiome composition and function with therapy and clinical outcomes leading to a better understanding of the lung microbiome and how this impacts on the well-being of patients with CF. LiPuma [29] showed the magnitude of changes in the CF lung microbiota around the time of exacerbation was found to be largely dependent on community diversity and composition at baseline. However, certain genera appear to play important roles in driving change in airway bacterial community composition at exacerbation. One limitation of the study by LiPuma was it was retrospective and they were unable to fully assess the relationship between exacerbation severity and changes in specific microbiota. Furthermore, that study did not evaluate antibiotic use, lung function measures, and clinical outcomes. This study intends to answer some of those questions by performing 16S microbiomic analyses. Using these modern molecular approaches, we will be able to assess whether inhaled antibiotics such as Cayston® induce different changes to the bacterial community structure than current IV antibiotics, thus allowing more potential treatment pathways and the development of new approaches.

2.1 Assessment and management of risk

This trial is categorised as: (delete as appropriate)

- Type B = Somewhat higher than the risk of standard medical care

See Appendix 1

Risks related to the study design:

After assessing the potential risk in this study, we consider the main potential risk is that our intervention may not provide the optimal treatment for an acute pulmonary exacerbation. There is little evidence in the use of inhaled antibiotics to treat acute exacerbations, however a recent trial, of similar design and conducted at this centre, found inhaled antibiotics can be effective in treating exacerbations and also significantly prolonged the time to next exacerbation. [14] With this evidence in mind and grounding in the theory that inhaled antibiotics can provide excellent lung delivery with reduced systemic effects, it is assessed that the risk in this trial compared to standard practice is small. In order to minimise this risk the protocol dictates daily review by the medical team and if it is felt that continuing on the investigational product is not in the participant's best interest then, after discussion with the participant, they will be immediately switched to two intravenous anti-pseudomonal antibiotics I.e. the current standard practice for treatment of pulmonary exacerbations of CF.

The CF population is very heterogeneous both phenotypically and genotypically. Hence, there presents a risk of inter-subject variability in treatment confounding results in a parallel study design. Utilising a cross-over design manages this risk and also makes the study more efficient by reducing the number of participants required to achieve an appropriate power. The main risk often associated with a cross-over design is carry-over effect but we feel that it is unlikely to be a factor in this study. Each treatment will only be given at the point of admission for exacerbation, therefore by default any significant benefit gained from the previous treatment no longer exists. The cross-over design will be particularly beneficial for the microbiomic analyses

as this will allow direct comparison of the effect of each treatment in every participant, with each participant acting as their own control. Admissions for intravenous antibiotics can be triggered for a variety of reasons and hence we have followed the advice of Bilton et al [30] and utilised a modified Fuch's criteria to define exacerbations qualifying for treatment in this study. These criteria will help standardise the variability that exists in the triggers and thresholds for admissions amongst patients and also their admitting physicians.

Risks related to the test IMP:

Other risks associated with this study are the risk of side effects from the test IMP itself. Cayston ® is generally well-tolerated but common side effects include nasal congestion, cough and wheeze/bronchospasm [31]. A test dose of Cayston® will be given by a specialist respiratory physiotherapist in order to assess patients for side-effects and if there is evidence of an exaggerated bronchoconstriction response then the subject will not proceed further in the study. To further minimise the risk of wheeze/bronchospasm a nebulised bronchodilator will be given prior to all Cayston® doses. The use of Cayston® for chronic suppression has been associated with decreased susceptibility of PA to Aztreonam in some cases [31], however in a large phase 3 study no changes in PA susceptibility to aztreonam were seen. Interestingly, increases in susceptibility to tobramycin were seen [32]. Given the much shorter course of treatment in this study it is unclear what effect this will have on susceptibility and hence antimicrobial resistance (AMR) will be assessed as a secondary outcome in order to allow us to answer this question. Cayston® is known to cross the placenta and enter foetal circulation in rats but did not demonstrate adverse reproductive effects in rats even in doses up to 750mg/kg/day [33]. The dose in this study is roughly 4.5mg/kg/day and hence we do not expect there to be any adverse reproductive effects. Nonetheless, given the lack of human reproductive toxicity data pregnant women will be excluded and all participants entering the trial will be advised on the need to use highly effective contraception for a defined period whilst receiving Cayston®. Contraceptive methods considered highly effective include:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

The period of time participants will be advised to continue with the above contraceptive measures will the length of their Cayston® treatment plus 24 hours, this will allow Cayston, as well as all comparator IMPs to be successfully excreted from the body in all participants, including those with renal or hepatic impairment.

Risks related to study investigations:

Blood tests will be taken on three occasions on each admission in this study, twice more than is the current standard practice. Blood tests inevitably involve some discomfort. To minimise this risk, vascular access devices e.g. midlines, central lines, Hickman lines will be used

wherever possible to obtain blood samples. In participants who do not have a long-term vascular access devices in-situ blood will be obtained by an appropriately trained person and if required numbing anaesthetic cream is available on all cystic fibrosis wards at Liverpool Heart and Chest Hospital. The benefit of the extra blood tests will be the ability to compare and contrast the pattern of biochemical markers of infection with the changes in microbiome community structure.

Spirometry will be performed regularly during admission in line with current standard practice. Spirometry is a generally safe, however there is a risk of feeling short of breath or dizzy for a few moments after performing the test. Given that Spirometry is a routine investigation that participants will be well accustomed with as part of their standard care we assess there is minimal risk associated with this investigation.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

This study's primary objective is to investigate whether there is immediate clinical benefit in the use of Cayston® in acute exacerbations of CF.

Null Hypothesis:

14 days of Cayston® plus IV Colistin for exacerbations of CF does not result in equivalent improvement in FEV1 when compared to IV Colistin and another standard IV anti-pseudomonal antibiotic.

Alternative Hypothesis:

14 days of Cayston® plus IV Colistin for exacerbations of CF does result in equivalent improvement in FEV1 when compared to IV Colistin and another standard IV anti-pseudomonal antibiotic.

3.2 Secondary objectives

Secondary objectives of this study are to answer the following questions:

- What effect Cayston® plus IV Colistin has on the microbiome, pseudomonal counts and antimicrobial resistance patterns in of patients with CF, as compared with two standard IV antibiotics?

- Are there sustained clinical benefits in using Cayston plus IV Colistin as compared with two standard IV antibiotics?

- Are there quality of life benefits in using Cayston plus IV Colistin as compared with two standard IV antibiotics?

3.3 Primary endpoint/outcome

Average actual change from Day 1 (start of exacerbation) in % predicted forced expiratory volume in 1 second (ppFEV1), the end of each arm of study (day 14)) (i.e. recovery of $ppFEV_1$ at each time point from day 1)

3.4 Secondary endpoints/outcomes

1. Time to first protocol-defined pulmonary exacerbation (or end point of 12 months if no subsequent exacerbation)
2. Average change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptom Scale (RSS) score at the end of each arm of study?
3. 16S microbiome, PA sputum counts and total bacterial load.
4. Prevalence of resistance to antibiotics and changes in antimicrobial resistance (AMR)

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective	Average actual change from Day 1 (start of exacerbation) in % predicted forced expiratory volume in 1 second ($ppFEV_1$) at 7 days, the end of each arm of study (day 14) (i.e. recovery of $ppFEV_1$ at each time point)	Spirometry at Day 1, 7, 14 & 28.
Secondary Objective	Time to first protocol-defined pulmonary exacerbation (or end point of 12 months if no subsequent exacerbation)	12 months
	Average change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptom Scale (RSS) score at the end of each arm of study	Day 1 and 14 of each arm.
	PA sputum counts, total bacterial load and 16S microbiome structure	Sputum taken on day 1 and 14
	Prevalence of resistance to antibiotics and changes in antimicrobial resistance (AMR)	Sputum sample taken on day 1 and 14

4 TRIAL DESIGN

To investigate the study hypothesis we will utilise a randomised crossover design. Upon their first admission with a protocol defined exacerbation participants will be randomised to first receive either: **14 days of Cayston® plus intravenous Colistin**

Or

14 days of a standard intravenous antibiotic plus intravenous Colistin

Upon their next exacerbation, participants will "crossover" to receive the treatment they did not receive on their previous exacerbation. Exacerbation will be defined as per the modified Fuchs criteria set out by the EuroCF working group in 2011:

Two or more of the following:

- Change in sputum volume or colour
- Increased cough
- Increased malaise, fatigue or lethargy
- Anorexia or weight loss
- Decrease in pulmonary function by 10% or more / Radiographic changes
- Increased dyspnoea [30]

5 STUDY SETTING

This study will be conducted as a single-centre study. The centre is Liverpool Heart & Chest Hospital NHS Foundation Trust (LHCH).

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Confirmed diagnosis of CF
2. Patients aged 16 - 65 years of age who can give informed consent
3. ppFEV$_1$ >25% or <75% predicted (in keeping with Cayston® prescribing license)
4. Admitted to the LHCH with an exacerbation of CF pulmonary disease as per the criteria defined in Section 4
5. Presence of PA in lower respiratory tract cultures in the 6 months prior to screening

6.2 Exclusion criteria

1. Documented allergy to beta-lactam antibiotics or IV Colistin
2. Growth of Burkholderia cepacia Complex (BCC) within 1 years
3. Pregnancy
4. Previous organ transplant
5. Receiving other clinical trial medication
6. Already prescribed regular Cayston®
7. Hypersensitivity reaction to Cayston excipient
8. Hypersensitivity reaction to polymixin B (Colistin)
9. Patients with myasthenia gravis
10. Any contraindication to the use of the chosen standard intravenous antibiotic.

7 TRIAL PROCEDURES

7.1 Recruitment & Patient identification

The CI, a CF Fellow at LHCH, will identify all potential participants from the register of patients attending the Adult CF unit at Liverpool Heart & Chest Hospital. A patient information sheet (PIS) will be posted to all eligible participants. Basic information on patients deemed ineligible will be kept in keeping with CONSORT. Potential participants will be asked to read the PIS and, if interested, will be asked to contact a member of the research team who can then arrange a further meeting. Alternatively, patients will be able to discuss the study with their usual medical practitioner at LHCH, who can then refer the patient to the research team via the PI. Sending the PIS out in advance will ensure that anyone who attends clinic and would like to enrol in the study but needs to be admitted the same day will not be excluded due to the fact they have not had at least 24 hours compulsory "cooling off" period to consider the study.

All inclusion and exclusion criteria are routinely available to medical practitioners at clinic appointments and hence the inclusion/exclusion criteria can be confirmed at this stage. A member of the research team will then arrange to discuss the study in more detail and answer any questions/concerns. If, after all questions have been answered, the participant wishes to enrol on the study the consent form will be completed with a physician member of the research team, who will formally confirm eligibility. The trust's social media outlets may also be used to disseminate information about the study. A record of all patients referred to the research team will be kept and will include anonymised information including age, gender, ethnicity, whether the patient went on to register with the trial and whether they went on to be randomised. Reasons, if given, for both opting against registration and for participants not being randomised will be documented.

7.2 Screening

Screening for patients eligible for this study will be carried out by the CI, CF Fellow in the Adult CF Centre at Liverpool Heart and Chest Hospital using the registry information for the unit. No new screening tests will be required to confirm eligibility/exclusion criteria. All inclusion/exclusion criteria will be checked in the database and if needed corroborated on the Trust's electronic patient record.

7.3 Consent

The consenting process will be carried out in accordance with GCP and Declaration of Helsinki principles. The recruiting process is outlined in 7.1.1. A physician member of the research team will carry out the consent process after assessing patients' understanding of the study and their capacity to make a decision regarding participation. Eligibility will then be formally confirmed. The consenting process will take place in the outpatient department at LHCH. Delegation of this role by the CI will be documented in the delegation log.

The consenting team member will clarify that the PIS has been read and discuss the study in further detail including answering questions or queries. The consent form will be explained and then if the participant is willing to proceed the form will be signed. A copy of the signed Informed Consent Form (ICF) will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate

At the time of writing, there are no patients in our adult CF cohort who require translation or specialist communication support. If it became apparent that this was necessary then we would seek the use of the Trust's contracted telephone translation service. Where a patient has consented to the trial and later becomes incapacitated such that they no longer have capacity but

their eligibility status remains unchanged, the original consent will remain in place but the participant would be withdrawn if their ability to complete the study assessments was hampered.

7.3 The randomisation scheme

Block randomisation in groups of four will be carried-out using Statsdirect® software(Statsdirect Ltd. 2013). The CI and/or trial co-ordinator will perform this prospectively and the allocation sequence will be printed and kept in a locked cabinet in the Research Centre at LHCH. The sequence will then be referred to as each patient is consented onto the study. As this study is not blinded there is no need for emergency break codes or out-of-hours access codes.

7.4 Baseline data

Baseline line data to be collected in this study is listed below:

- Height, Weight, BMI
- Age
- Gender
- Race
- Smoking/Alcohol history
- Co-morbidities
- Current medications and previous medications including detailed antibiotic history
- Blood tests (FBC, U&Es, CRP, LFTs – these will be performed at the start of each arm as documented previously)
- ECG
- CXR
- Spirometry
- Bronchoconstriction response to test dose of Cayston®

7.5 Trial assessments

Initial clinic		• Consent • Spirometry* • Cayston® test dose (this may occur at a convenient time after initial clinic)
Admission 1	**Day 1**	• Start first treatment – 14 day course of IV Colistin PLUS either Cayston® or another IV antibiotic* • Blood Tests* • Sputum Sample* • CFQ-R questionnaire
	Day 7	• Spirometry* • Blood tests
	Day 14	• Complete first treatment • Blood tests • Spirometry* • Sputum sample • CFQ-R questionnaire
		•
Admission 2	**Day 1**	• Start second treatment – 14 day course of IV Colistin PLUS either Cayston® or another IV antibiotic* • Blood Tests* • Sputum Sample* • CFQ-R questionnaire
	Day 7	• Spirometry* • Blood tests
	Day 14	• Complete first treatment • Blood tests • Spirometry • Sputum sample • CFQ-R questionnaire
		•

7.6 Long term follow-up assessments

. Using the trusts electronic patient record there will be surveillance of participants' hospital admissions over the 12 months following completion of each arm of treatment with the time to next admission being recorded as a secondary outcome measure.

7.7 Withdrawal criteria

The circumstances in which participants will be withdrawn from the study or test IMP treatment are listed below:

- Participants may at any time withdraw themselves from the study
- The medical team including the participants' usual physician may at any time withdraw a participant from the study/IMP treatment if they feel that continuing is not in the patient's best interests (i.e. poor response to treatment or deteriorating clinical parameters).
- If new information/evidence comes to light regarding any IMPs that changes the safety profile or suggests significantly increased risk to any participant.
- Severe bronchoconstriction reaction seen following test dose of Cayston®.

In cases where participants were receiving the test IMP treatment when withdrawing from the study they would immediately be switched to two IV anti-pseudomonal antibiotics, the choice of which would be made in conjunction with the participant and their medical team. All participants would, with their consent, continue to part of the study as long as they had received any IMP treatment with the exclusion of the test dose. Participants who withdraw but had not received any IMP treatment or had received just the test dose would no longer be part of the study, would not receive any further follow up, would not be included in statistical analysis and would be replaced by new participants. A withdrawal log will be kept including reasoning and details of withdrawal.

7.8 Storage and analysis of samples

Sputum:

- Collection: Sputum will be collected from patients into universal specimen tubes at the times specified in the timeline. Specimen containers will be collected by the research team and will be labelled anonymously with patients unique trial number, study arm (first or second) and sample type (i.e. start or end of treatment).

- Storage: After collection, samples will be taken to the research laboratory at LHCH where, within 24 hours, they will be separated into pre-labelled 2ml plastic aliquots and frozen at -80 degrees Celsius.

- Analysis: Once all 64 sputum samples are collected the samples will be taken in a frozen travel box via taxi to University of Liverpool. The taxi courier will be arranged by the sponsor. Analysis using 16S dual nested PCR and subsequent next generation sequencing (NGS) will be undertaken at the University. Analysis of the results will be performed using the Quantitative insights into Microbial Ecology (QIIME) software.

- Destruction: Samples will be destroyed at the end of the study, unless there is a new application to the HRA or Human Tissue Authority with regards to their future use.

Blood:

- Blood tests will be collected by a member of the usual medical or research team. As blood markers are not an outcome in this study and will be used only as a comparator, samples will not be labelled anonymously and will be labelled and processed as per usual trust protocols before being transported to the Pathology Lab at LHCH, where they will be stored and analysed as per usual Lab procedure.

All samples will be appropriately labelled in accordance with the trial procedures to comply with the 1998 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.9 End of trial

The trial will be completed once all participants have met one of the two criteria below:

a) Subsequent exacerbation requiring admission after completing both treatment phases of the study.
b) 12 months have passed since completion of both treatment phases of the study.

The sponsor will notify the MHRA and REC within 90 days of completion.

8 TRIAL MEDICATION

8.1 Name and description of investigational medicinal products (IMPs)

Test IMP**:**

IMP:	Aztreonam
Brand name:	Cayston®
Form:	Powder and solvent for nebuliser solution
Dose:	75mg TDS
Status:	Full EMA marketing authorisation for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa.*
MA Holder:	Gilead Sciences International Ltd
MA numbers:	EU/1/09/543/001 EU/1/09/543/002

Comparator IMPs:

IMP:	Colistin
Brand name:	None specified
Other name:	Colistimethate sodium
Form:	Powder for solution for infusion
Dose:	2million international units TDS

IMP:	Meropenem
Brand:	None specified
Other name:	N/A
Form:	Powder for solution for infusion
Dose:	1g TDS

IMP:	Piperacillin/Tazobactam
Brand:	None specified
Other name:	N/A
Form:	Powder for solution for infusion
Dose	4.5g TDS

IMP:	Ceftazidime
Brand:	None specified
Other name:	N/A
Form:	Powder for solution for infusion
Dose:	3g TDS

IMP:	Aztreonam
Brand:	None specified
Other name:	N/A
Form:	Powder for solution for infusion
Dose:	2g TDS

IMP:	Fosfomycin
Brand:	None specified
Other name:	N/A
Form:	Powder for solution for infusion
Dose:	4g TDS

8.1.2 Dose Rationale

Dose for the test IMP was selected based on its current licensed dose. Course length was selected to mirror CF trust guidelines for antibiotic treatment of exacerbations in CF The dosages for the comparator IMPs are based upon licensed doses and those recommended by a combination of the CF Trust guidelines and local formulary,[34]

8.2 Legal and regulatory status of the drugs

Cayston®, has a full MA for the suppressive therapy of chronic pulmonary infections due to *PA.* However, given that is being used for the treatment of acute infection in this study it is being used outside of its authorisation and hence the trial is being carried out under a CTA. The drug is therefore only to be used by the named investigators, for the patients specified in this protocol, and within the trial. Colistin, also known as Colistimethate, has a licensed indication for the management of severe gram negative infections. It has been designated as an IMP rather than a background NIMP as although it is being used in both arms of the study, the complex nature of microbial colonisation in CF means that we cannot rule out a synergistic or inhibitory relationship of any other IMP and Colistin. For example, Cayston® and Colistin may act synergistically in that Cayston® may have an effect that makes a subset of bacteria more susceptible to Colistin, in this case some of the clinical difference seen would actually be attributable to Colistin and hence it cannot be termed a background NIMP. Conversely, theoretically another intravenous IMP may have an antagonistic effect on Colistin® and reduce the clinical effects seen. The difference between the treatment effects compared to the nebulised arm would not be entirely attributable to Cayston® and hence Colistin would actually be more appropriately termed a comparator. All other comparator IMPs have licensed indications for broncho-pulmonary infections in cystic fibrosis, severe gram-negative pulmonary infections and lower respiratory tract infections. All comparator IMPs are recommended for use in the CF Trust Antibiotic Treatment guidelines.[34]

8.3 Summary of Product Characteristics (SmPC)

The Test IMP Cayston® has a full marketing authorisation for the chronic suppression of pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis. The AZTEC-CF study aims to pilot its use in acute exacerbations using an unmodified formulation and the dosing

regimen for which the MA is held. As such, in accordance with Section 2.7.3.2 *EU directive 2001/20/EC "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trials*", an IMP dossier is not required and instead relevant information is presented in the SmPC (Annexe 1). All comparator IMPs SmPCs are presented in Annexes 3-8.

8.4 Drug storage and supply

Cayston® will be manufactured and shipped free of charge by the funder (Gilead Sciences, UK) who will also supply 16 Altera® nebuliser systems. 705 vials of Cayston® (672 for the study plus 5% overage) and 16 Altera® nebuliser systems will be provided. The shipment will be split in two, with the first shipment at the start of the study and the second shipment half-way through. The shipment will be normal commercial stock with a commercial label. The drug will be delivered to the research pharmacist at Liverpool Heart and Chest Hospital, where it will be labelled with trial specific labels. Storage will be in keeping with the SPC, namely stock will be kept refrigerated at 2^{o}C-8^{o}C. Once a patient enrolled on the trial is admitted with acute pulmonary exacerbation a specific trial prescription of Cayston® will be made on the inpatient electronic prescription system. At this point Cayston® and Altera® nebuliser system will be supplied from pharmacy to the relevant ward where it will continue to be refrigerated. All refrigerators used in this study will be monitored daily with calibrated thermometers. The medication will be reconstituted by the ward nursing staff who will then oversee the administration of Cayston® via the Altera® nebuliser system.

At the completion of the Cayston® treatment arm, Cayston® will be discontinued. If there is on-going need for antibiotics then the medical team will select two intravenous anti-pseudomonals to continue. The participation in this trial does not affect subjects' eligibility for Cayston® as long-term suppressor therapy in the future. Cayston® would not routinely be prescribed again in the acute setting as it is currently unlicensed for this indication.

All comparator IMPs will be provided by the Sponsor from the general stock of the Pharmacy Department. All storage will be in accordance with the SmPC of each individual product. As mentioned previously this protocol does not dictate which brand of comparator IMP is used as long as the active substance remains the same. This policy has been adopted to allow for temporal changes in suppliers/manufacturers of the comparator IMPs.

8.5 Preparation and labelling of Investigational Medicinal Product

Cayston® will be shipped to LHCH in its usual commercial form with britestock packaging and labelling. Labelling with trial specific labels (figure 1) will be undertaken in the pharmacy at LHCH. All comparator IMPs will be labelled in the pharmacy department before being transferred to the relevant ward for storage and administration. Examples of labels are provided below. All comparator IMPs will be prepared and administered in accordance with the SmPC.

Figure 1: Labels IMPs

The test IMP Cayston® will be prepared and administered in accordance with the SmPC (Box 1).

Box 1: Cayston® preparation instructions (as adapted from the SmPC)

Preparing your Cayston for inhalation

- Do not prepare Cayston until you are ready to administer a dose.
- Do not use Cayston if you notice that the package has been tampered with.
- Do not use Cayston if it has been stored outside a refrigerator for more than 28 days.
- Do not use the solvent or prepared Cayston if it is cloudy or if there are particles in the solution.

1. **Take one amber vial of Cayston and one ampoule of solvent** from the box. Solvent ampoules must be separated by gently pulling them apart.
2. **Gently tap the amber vial** containing the Cayston so that the powder settles at the bottom. This helps to ensure that you get the proper dose of medicine.
3. **Open the amber vial:** tear and flip up the blue cap or lift up the metal flap on the top (Box 2: Figure 1a) and pull down (Box 2: Figure 1b) to carefully remove the entire metal ring and overcap from the vial (Box 2: Figure 1c). Safely dispose of the ring. Carefully remove the rubber stopper.
4. **Open the ampoule of solvent** by twisting off the tip. Squeeze out the contents completely into the vial (Figure 1d). Next, gently swirl the vial until the powder has completely dissolved and the liquid is clear.

Preparing the Altera Nebuliser to take your Cayston

1. **Make sure the Altera Nebuliser Handset** is on a flat, stable surface.
2. **Remove the medicine cap** by twisting anticlockwise.
3. **Pour all of the prepared Cayston from the vial** into the Altera Nebuliser Handset medicine reservoir (Box 3: Figure 2a). Be sure to completely empty the vial. Gently tap the vial against the side of the medicine reservoir if necessary.
4. **Close the medicine reservoir** by aligning the tabs of the medicine cap with the slots on the reservoir. Press down and turn the cap clockwise as far as it will go (Box 3: Figure 2b).

Using the Altera Nebuliser to take your Cayston

1. **Begin your treatment.** Sit in a relaxed, upright position. Hold the handset level and place the mouthpiece in your mouth and close your lips around it.

Box 2:

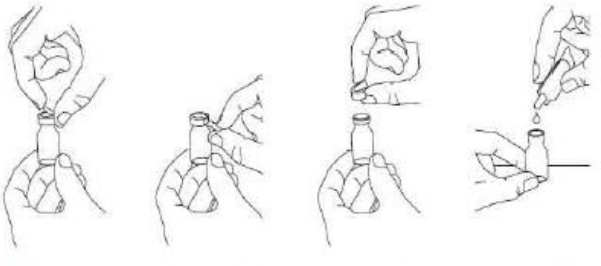


Figure 1a Figure 1b Figure 1c Figure 1d

Box 3:

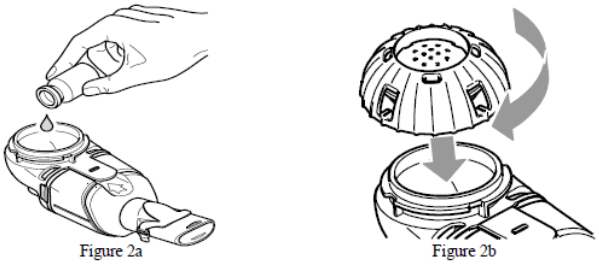


Figure 2a Figure 2b

8.6 Dosage schedules

The dosing schedule for Cayston® will be one dose (75mg) three times a day for a total of 14 days. The timings will be morning, afternoon and evening (0800, 1400 & 2200). Doses will be administered using the Altera Nebuliser Handset ®. A short acting bronchodilator and any prescribed mucolytics will be administered prior to each dose in accordance with the SPC.

8.7 Dosage modifications

There are no dosage modifications planned in this study.

8.8 Known drug reactions and interaction with other therapies

There are no known drug interactions for Cayston®. [31]

8.9 Concomitant medication

Patients who are already prescribed Cayston® as chronic suppressor therapy will be excluded from this study. Patients who have recently (< 3months) been commenced on disease modifiers such as ivacaftor will be not be permitted to enrol in the trial. Patients who have been on disease modifiers for > 3months will be permitted. Other trial medications will not be permitted during this study to avoid unexpected interactions and potential confounding of results.

8.10 Trial restrictions

As mentioned previously advice will be given regarding contraception to all participants see section 2.1.

8.11 Assessment of compliance

Overall compliance will be assessed using the electronic patient record (EPR) (AllScripts™, AllScripts UK, Manchester) used at Liverpool Heart & Chest Hospital. Cayston® will be provided three times a day on a dose-by-dose basis to participants by nursing staff. Patients will then administer the dose themselves, witnessed by nursing staff who will then record the administration accordingly in the EPR. Compliance will be routinely checked by a member of the research team on day 7 of each admission and again at day 14. An assessment of compliance including all missed doses will be recorded in the CRF with reasons for missed doses where possible.

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

9.2 Operational definitions for (S)AEs

Adverse events will be recorded in the medical records and CRF following consent. If the investigator suspects that the subjects' disease has progressed faster due to the administration of an IMP, then he will record and report this as an unexpected adverse event. A variety of well-recognised potential adverse reactions of the IMPs are listed in the SmPC (see annexe 2-8) and these reactions will be recorded but not reported immediately unless serious or unexpectedly severe. Clinically significant abnormalities in the results of objective tests (e.g. bloods, spirometry) will also be recorded as adverse events. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. Events will be reported via the Sponsor's reporting form as per the trust SOP. All adverse events will be recorded until the day of completion of each trial arm. All adverse events, aside from those recognised in the SPC, will be reportable to the Sponsor up to 14 days post last IMP administration. When determining the expected nature of SAEs, section 4.8 of the SmPCs will be referred to in order to provide Reference Safety Information (RSI).

9.3 Recording and reporting of SAEs AND SUSARs

All SAEs/SUSARs occurring from the time of start of trial treatment until 1 day post cessation of trial treatment must be recorded on the Sponsor's "Adverse Event Reporting Form" (Appendix 2 & 3) and delivered to the Sponsor within 24 hours or 7 day (of research team becoming aware) for SUSARs and SAEs respectively. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAE/SUSAR the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached."

All SAEs assigned by the CI or delegate as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor will inform the MHRA, the REC and the Sponsor of SUSARs within the required expedited reporting timescales.

9.4 Responsibilities

Chief Investigator (CI) or delegate:

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness and causality using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.
4. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
5. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
6. Using medical judgement in assigning expectedness.
7. Immediate review of all SUSARs.
8. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
9. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
10. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a MACRO database.
2. Reporting safety information to the CI or delegate for the ongoing assessment of the risk benefit.
3. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
4. Notifying Investigators of SUSARs that occur within the trial.
5. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
6. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Given the small nature of this study, at one centre, with limited follow up period, a Data Management Committee (DMC) and Trial Steering Committee (TSC) will not be created. Instead the day to day running of the trial will be managed by the Study Team, who will also be responsible for recruitment, safety monitoring, protocol adherence and regulatory report submission. The study will be regularly discussed at monthly research team meetings, where recruitment progress, SUSARs/SAEs and protocol issues will be discussed.

9.5 Notification of deaths

Deaths that are assessed to be caused by an IMP will be reported to the sponsor. This report will be immediate.

9.6 Pregnancy reporting

All pregnancies within the trial will be reported to the CI and the Sponsor using the Pregnancy Reporting Form (Appendix 4) within 24 hours of notification. If the pregnant party is the trial participant, then no further active participation in the trial will take place with immediate effect. If the pregnant party is a trial participant's partner then a discussion between the participant, and CI (or delegate) will be undertaken to ascertain whether on-going participation is appropriate. Monitoring and follow up all pregnancies will take place via at least 3 monthly follow up appointments in the outpatient department for 12 months. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity [31] and hence follow up beyond initial post-partum phase is not felt to be required. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

9.7 Overdose

Prescription and administration data will be recorded on the electronic patient record (AllScripts™, AllScripts UK, Manchester) used at Liverpool Heart & Chest Hospital. This system utilises an electronic prescription system, which does not permit the administration of doses or frequency above those prescribed and hence significantly reduces the risk of overdose. The medical team will review the drug charts daily and any overdoses will be reported to a member of the research team, who will then record the overdose in the deviation log. The sponsor will be notified of all deviations every 3 months. All SAEs associated with an overdose will be reported accordingly. Our assessment is that the risk of overdose is extremely low, given that all IMPs will be prescribed electronically and all IMP administration will be carried out under supervision of trained nurses in an in-hospital setting.

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.9 The type and duration of the follow-up of subjects after adverse events.

Adverse events and reactions will be recorded for one day following the last dose of the IMP administered. The ward medical team will undertake immediate care following an adverse event or reaction. Follow-up will be at 14 days following the last dose of the IMP, at which point an assessment of the resolution of any reaction will be made and further follow-up, if required, will be arranged. Any SUSAR related to an IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred

9.10 Development safety update reports

The sponsor will submit DSURs once a year throughout the clinical trial, or on request to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor. The

report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

Due to the pilot nature of this study we have not included a formal power calculation.

10.2 Planned recruitment rate

We expect to recruit 50% of patients by April 2017 and 100% of patients by August 2017.

10.3 Statistical analysis plan

Provided by Matt Shaw, Senior Clinical Information Analyst, Liverpool Heart and Chest Hospital (see Annexe

10.3.1 Summary of baseline data and flow of patients

Baseline line data to be collected in this study is listed below:

- Height, Weight, BMI
- Age
- Gender
- Race
- Smoking/Alcohol history
- Co-morbidities
- Current medications and previous medications including detailed antibiotic history
- Blood tests (FBC, U&Es, CRP, LFTs – these will be performed at the start of each arm as documented previously)
- ECG
- CXR
- Spirometry
- Bronchoconstriction response to test dose of Cayston®

10.3.2 Primary outcome analysis

- Percentage FEV1 will be recorded on Days 1, 7, 14 and 28 post index exacerbation. Data will be recorded as a continuous variable. Paired t-tests and repeated measures ANOVA tests will be used to compare results between the randomised groups.
- Any missing data due to non-compliance, incorrect recording or patient withdrawals will be replaced using multiple imputation.
- Data will be reported and analysed on an intention to treat (ITT) basis

10.3.3 Secondary outcome analysis

This study has 3 secondary outcomes. Regarding the microbiomic analysis, this will be performed using the Quantitative insights into Microbial Ecology (QIIME) software to assess changes in structure, richness and diversity. The other outcomes include pseudomonal counts/antimicrobial resistance, clinical benefits and patient quality of life measure. In each of these cases, continuous data comparisons will be made using paired parametric (paired t-test) or non-parametric (Wilcoxon signed ranks) tests. Comparisons between categorical paired data will be made using the McNemar adjustment to the chi-squared test. 95% confidence limits will also be estimated for visual inspection

10.4 Subgroup analyses

No subgroup analysis is planned for this study.

10.5 Adjusted analysis

No adjustment analysis is planned for this study.

10.6 Interim analysis and criteria for the premature termination of the trial

No interim analysis is planned for this study.

10.7 Subject population

All study participants will be reported on and analysed as initially randomised.

10.8 Procedure(s) to account for missing or spurious data

Any missing data will be estimated using multiple imputation techniques.

10.9 Other statistical considerations.

This trial has no special cause statistical considerations.

Any deviation from the statistical plan will be fully agreed by the trial team and any independent overseers whose judgment and approval may be required.

11 DATA HANDLING

11.1 Data collection tools and source document identification

Source data will include all data relevant to baseline tests, primary and secondary outcomes mentioned previously in this protocol. The source documents will be the clinical records on the EPR at Liverpool Heart & Chest Hospital (includes blood test results, Spirometry, medical team records) the CFQR paper questionnaires, a database of results from the microbiome analysis, PA counts and AMR work to be undertaken and the CRF (some data may be transcribed directly to CRF).

Data will be collected from the above source documents onto the CRF and then entered onto the trial database. EPR will be used to transcribe results, spirometry and other metrics, for example recent antibiotic use onto the CRF. A Trials Folder will be kept in the research centre at Liverpool Heart and Chest Hospital which shall include CRF and paper questionnaire results. The folder will be kept in a locked cabinet in the research centre.

11.2 Data handling and record keeping

The main trial database will be created using Microsoft Access software. This will be saved securely on a shared drive of the LHCH IT system but will be in approved-access only area and be password protected. Regular backed up copies will be made and also saved securely. Data in the main database will be transcribed from the CRFs. Data entry will be undertaken by the PI. A second database will be maintained at the University of Liverpool for the results specific to the microbiological analysis relevant to the secondary outcomes of this study. As samples will be anonymised before transfer to the University of Liverpool, the database maintained there will not contain any identifiable information. Participants' samples will only be identified by individual trial number and hence this will be identifier in that database. At the time of final data analysis, the anonymised second database will be brought to LHCH on an encrypted USB data drive. Dr Freddy Frost will be responsible for the data entry and quality of the database. Data analysis will be the responsibility of the Analyst team in LHCH Research Department.

11.3 Archiving

Trial documentation will be kept archived in its secured drive as per trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.

Destruction of essential documents will require authorisation from the Sponsor.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Research Ethics Committee (REC) review & reports

This trial will seek REC approval for the trial protocol, consent forms, PIS, GP letters, and Posters. Any substantial amendments will not be implemented until a favourable REC review. All REC correspondence will be kept in the trial folder. An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared. The REC will be notified of the end of the study and a final report of results will be submitted within one year of the end of the study.

12.2 Peer review

The funding for this trial was awarded by Gilead Sciences after a competitive application process. As part of the process the proposed protocol was reviewed by a cross-functional committee which considered the protocol along with the scientific merit of the proposal, no significant protocol alterations were suggested. The study has also been reviewed by local R&I committee and CF Research Committee at LHCH.

12.3 Public and Patient Involvement

Patients have been consulted informally in the outpatient department and it is clear that the idea of inhaled antibiotics for acute exacerbations addresses a number of points important to patients, namely time consumed by therapies, requirements of inpatient admission to treat all exacerbations and therapeutic options. Furthermore the SURE group, a patient representative group, at Liverpool Heart and Chest Hospital have been involved in the design of the study as well as the design of the trial documentation including the consent form and PIS. SURE has approved the final trial documentation for use. Findings will be disseminated using the hospital's research webpage as well as using the trust's social media channels.

12.4 Regulatory Compliance

This trial will not commenced until a CTA is obtained from the MHRA, the protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

12.5 Protocol compliance

All protocol deviations will be recorded in the deviation log and reported to the CI and Sponsor. Any frequently recurring deviations will be reviewed and a documented corrective plan will be implemented.

12.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach, which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

12.7 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. After participants have been enrolled they will be given a study number and from then onwards all data will be depersonalised. All personalised data will be kept in a locked cabinet in the research centre at Liverpool Heart and Chest Hospital, which is accessible only by an approved ID badge. All databases and digital data will be kept in a password-protected folder on the trusts shared IT shared drive. Any data, analysis or results transmitted to sponsors and co-investigators will not include identifiable data and will refer to study number only.

12.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

There are no known competing interests or commercial conflicts that may influence the running of this trial.

12.9 Indemnity

Liverpool Heart & Chest Hospital NHS Foundation Trust (LHCH) holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that LHCH has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. LHCH does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of LHCH or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

12.10 Amendments

It is the responsibility of the CI to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients. All substantial amendments (as decided by the PI) in concordance the HRA guidance. [35] Amendments will be communicated to the Sponsor, REC and MHRA for approval. The most up to date protocol will be saved in the trial master file, with all previous versions saved in a backup folder.

12.11 Post-trial care

Participants will receive their usual standard of care from the Adult CF team at LHCH after the trial has been completed. Future exacerbations would by default treated with standard therapy of two intravenous anti-pseudomonals.

12.12 Access to the final trial dataset

Access to the final dataset will be granted to:

- Chief Investigator
- Collaborators
- Sub-investigators
- Trial co-ordinator
- Trial statistician

13 DISSEMINIATION POLICY

The data arising from the trial will belong to the Adult CF Unit at Liverpool Heart & Chest. On completion the data will be analysed and a final study report prepared and sent to the REC and MHRA. Results will be submitted to scientific meetings and journals including but not limited to the European Cystic Fibrosis Society meeting, North American CF meeting and the Journal of Cystic Fibrosis. Results may be publicised on the trusts research centre website as well as via the trusts various social media channels. Participants who have indicated they wish to be informed of results directly will be sent a “layman” summary of the study report. Acknowledgement of Gilead Sciences as the funder will be made in all publications. Thanks to the University of Miami for permissions with regards to the CFQ-R will also be made in all publications.

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APPENDICES & ANNEXES – LIST OF CONTENTS

15.1 Appendix 1

Risks associated with trial interventions

☐ LOW ≡ Comparable to the risk of standard medical care

☒ MODERATE ≡ Somewhat higher than the risk of standard medical care

☐ HIGH ≡ Markedly higher than the risk of standard medical care

Justification:

Due to the use of Cayston® in a slightly new indication,we assess that the risk in this study is somewhat higher than the risk of standard medical care. Although, safety and tolerability will remain unchanged, there is a risk that Cayston® may not be as effective as standard medical care.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Cayston®	Lung function	Spirometry	Day 1,7, 14 & 28 of each arm	
	Clinical improvement	Medical review	Daily medical team review	

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

15.2 Adverse Event Reporting Form

Hospital number: _____ DOB: ___/___/_____ Event Date __/__/____

Study protocol Version and research number: _____

(as provided by the Clinical Quality department on Trust approval**)**

Short Study Name _____

Patient study number: _____

Chief Investigator name: _____

Consent date: _____

Procedure date: _____

Event date: _____

Adverse event number _____

(Consecutive numbers for each study)

Type of Adverse event (see flow chart)

Definition of an SAE/SUSAR

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalisation or **prolongation of existing hospitalisation** (standard length of stay should be stated in the protocol)
- Results in persistent or significant disability/incapacity

Or

- Is a congenital anomaly/birth defect

A Suspected, Unexpected Serious Adverse Reaction (SUSAR) Is an unexpected SAE that is related to the

Is this a Serious Adverse event? Yes/No

Is this a Suspected Unexpected Serious Adverse Reaction? Yes/No

Brief description of event (200 words max) including action taken:

_____

_____

Medication 24hours prior and after event (please continue on further page if necessary)

_____

_____

Causality

Unlikely to be due to research intervention ☐
Possibly due to research intervention ☐
Probably due to research intervention ☐
Definitely due to research intervention ☐

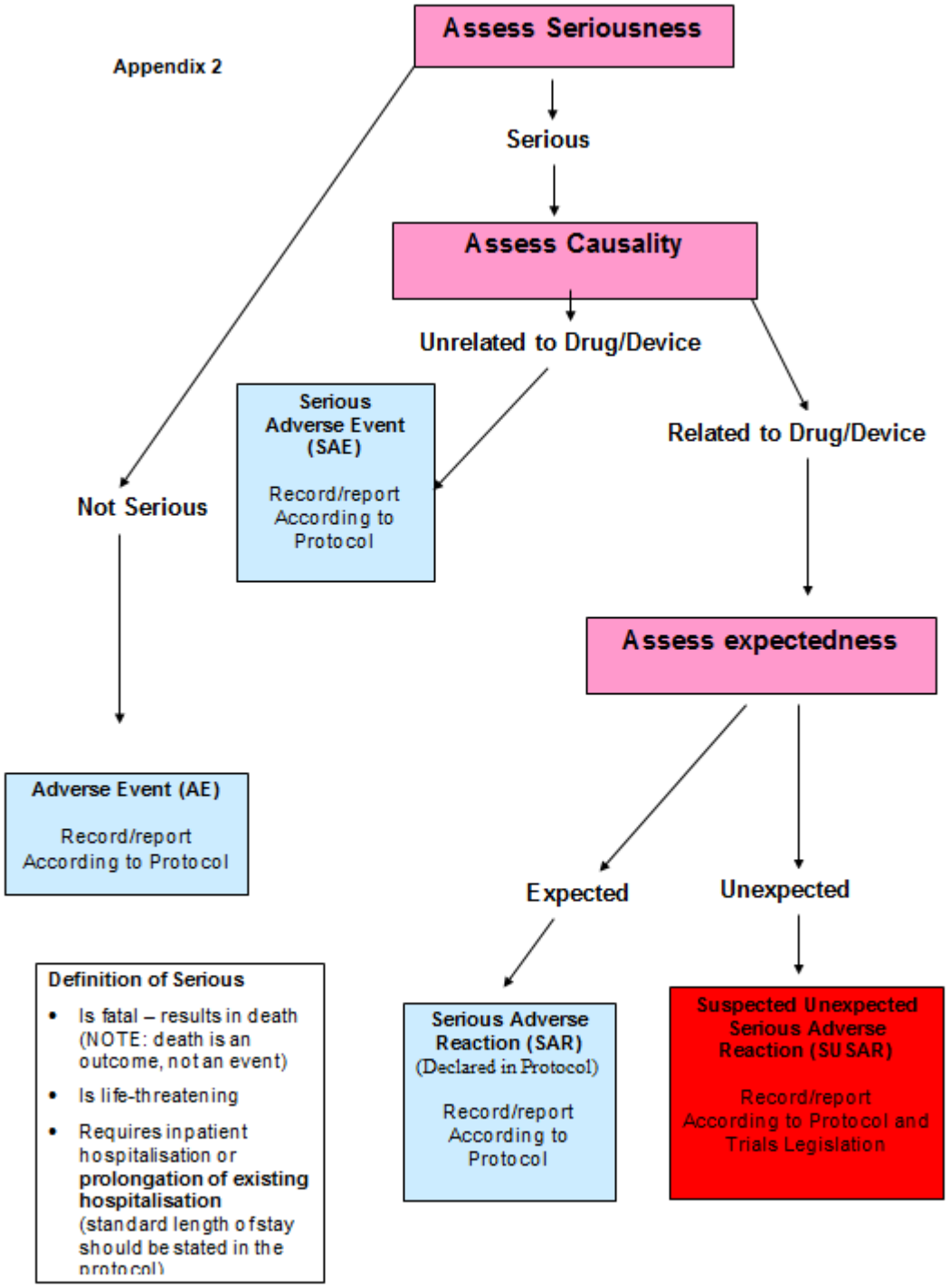
Outcome

Recovered ☐ Reported to Risk Management (LHCH)
Yes/No ☐
Recovered still under treatment ☐
Recovered with sequalae ☐ Date ----------
Permanent disability or disease
Death

Signature…….. Date……

Now take this form to the Clinical Quality Department within 7 days for an SAE and within 24 hrs for a SUSAR

15.3 Appendix 3 – Safety Reporting Flow Chart



15.4 Appendix 4 – Pregnancy Reporting Form

PREGNANCY REPORTING FORM

Liverpool Heart & Chest Hospital

Once you have become aware of a Participant or spouse pregnancy, please complete, scan & email/fax this signed form to the study sponsor WITHIN 24 hours of learning of the pregnancy.

Report type:	Initial □ Follow up □
Full title of the study:	
Sponsor R&D Number:	EudraCT Number:
MREC Number:	
Chief Investigator:	Name: Phone No: Email address:
Is this a double blind study?	Yes No
	If Yes are the code break procedures in place with pharmacy? Yes No
Name of ALL IMPs and/or medical devices	IMP 1: IMP 3: IMP 2: IMP 4:

This section should be completed by the SITE:

Subject identification code: Subject or partner : If partner date of consent (for pregnancy and outcome follow up:	Patient/initials (first, last):	_____
DOB: (Day/Month/Year) (___ /___/____)	Sex:	M □ F □
Patient's Age:		

Principal Investigator:	Name: Phone No: Email address:
Trial Co-ordinator local site:	Name: Phone No: Email address:
Name of reporting host institution:	Trust/ Institution name: Site number:

Date of site becoming aware of the event	___/___/____	
1. MATERNAL INFORMATION		
Date of Birth		
Date of last menstrual period		
Expected Date of Delivery		
Method of contraception:		
Contraception used as instructed?	Yes	
	No	
	Uncertain	

2. MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy.)

3. PREVIOUS OBSTETRIC HISTORY (provide details on all previous pregnancies, including termination or stillbirth

	Gestation week	Outcome including any abnormalities
1.		
2.		
3.		
4.		

4. DRUG INFORMATION (list all therapies taken prior to and during pregnancy)

Name of drug	Daily Dose	Route	Date Started	Indication	Date Stopped	Treatment Start (week of pregnancy	Treatment Stop (week of pregnancy)

5. PRENATAL INFORMATION

Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far	Yes		No		Not known	
	If yes, please specify:					
	Test:				Test Date:	
	Result:					

6. PREGNANCY OUTCOME	**Please ensure to collect and report this information to the sponsor within one week of outcome OR within 24 hours if an adverse outcome is learnt**

(a) Miscarriage Yes No		(b) Delivery Yes No	
If Yes:		If Yes	
Termination of pregnancy		Normal	
Planned		Forceps/Ventouse	
Spontaneous		Caesarean If yes please specify elective or emergency	
Please specify the reason and any abnormalities (if known):		Maternal complications or problems related to birth:	
Date of miscarriage:		Date of Delivery:	
Gestational age at miscarriage:			

7. MATERNAL PREGNANCY ASSOCIATED EVENTS

If the mother experiences an SAE during the pregnancy, please indicate here and complete an SAE form and submit to JRMO immediately.

8. CHILD OUTCOME

Congenital Abnormalities	Yes/No	Stillbirth	
If any congenital abnormalities, please specify			

				If yes specify date
Admission to neonatal intensive care unit	Yes/No			
If YES reason for admission to the unit				
Neonatal death	Yes/No			
Sex:				
Head circumference: cm	Apgar Scores:	1 min		
Weight¨ kg		5 mins		
Height: cm		10 mins		
10. ASSESSMENT OF SERIOUSNESS (OF PREGNANCY OUTCOME)				
Life-threatening	Mother died		Stillbirth/neonate died	
	Date of death		Date of death	
Involved prolonged inpatient hospitalisation				
Results in persistent or significant disability/incapacity				
Other seriousness criteria:	Congenital anomaly/birth defect		Other significant medical Events:	
11. ASSESSMENT OF CAUSALITY(OF PREGNANCY OUTCOME) Please indicate the relationship between pregnancy outcome				
Is the SAE **likely** to be a reaction to one of the IMPs with in the trial?	IMP X likely or possibly **Related** □ Unrelated □			
12. ADDITIONAL INFORMATION:				
Person completing the form				
If not the CI specify Name:				
Phone No:	Email address:		Signature: Date:	
Investigator's Name (PLEASE Print) :				

Investigator's Signature Date:

For R&D Office use only

Date form RECEIVED by R&D team: (___ /___/____)	Reviewed by: Date reviewed:
For SUSAR only:	Date reported to the MHRA:

15.5 Appendix 6 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.

ANNEXE 1:

Cayston® SmPC

1. NAME OF THE MEDICINAL PRODUCT

Cayston 75 mg powder and solvent for nebuliser solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains aztreonam lysine equivalent to 75 mg aztreonam. After reconstitution the nebuliser solution contains 75 mg aztreonam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for nebuliser solution.

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Patients should use a bronchodilator before each dose of Cayston. Short acting bronchodilators can be taken between 15 minutes and 4 hours and long acting bronchodilators can be taken between 30 minutes and 12 hours prior to each dose of Cayston.

For patients taking multiple inhaled therapies, the recommended order of administration is as follows:

1. bronchodilator
2. mucolytics
3. and lastly, Cayston.

Adults and children 6 years and older

The recommended dose for adults is 75 mg three times per 24 hours for 28 days.

Doses should be taken at least 4 hours apart.

Cayston may be taken in repeated cycles of 28 days on therapy followed by 28 days off Cayston therapy.

The dosing in children aged 6 years and older is the same as for adults.

Elderly

Clinical studies of Cayston did not include Cayston-treated patients aged 65 years and older to determine whether they respond differently from younger patients. If Cayston is to be prescribed to the elderly then the posology is the same as for adults.

Renal impairment

Aztreonam is known to be excreted renally and therefore administration of Cayston in patients with renal impairment (serum creatinine > 2 times upper limit of normal) should be undertaken with caution. No dose adjustment is necessary in cases of renal impairment since the systemic concentration of aztreonam following inhaled administration of Cayston is very low (approximately 1% of the concentration resulting from a dose of 500 mg aztreonam for injection).

Hepatic impairment

There are no data on the use of Cayston in patients with severe hepatic impairment (ALT or AST greater than 5 times the upper limit of normal). No dose adjustment is necessary in cases of hepatic impairment.

Paediatric population

The safety and efficacy of Cayston in children younger than 6 years of age have not been established. Currently available data are described in section 5.1 but no recommendation on posology can be given.

Method of administration

For inhalation use.

Cayston should only be used with the Altera Nebuliser Handset and Altera Aerosol Head connected to an eBase Controller or an eFlow rapid Control Unit. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Allergic reactions

If an allergic reaction to aztreonam does occur, stop administration of the medicinal product and initiate treatment as appropriate. The occurrence of rash may be indicative of an allergic reaction to aztreonam.

Cross-reactivity may occur in patients with a history of allergy to beta-lactam antibiotics, such as penicillins, cephalosporins, and/or carbapenems. Animal and human data demonstrate low risk of cross-reactivity between aztreonam and beta-lactam antibiotics. Aztreonam, a monobactam, is only weakly immunogenic. Caution is advised when administering Cayston to patients if they have a history of beta-lactam allergy.

The following rare and severe adverse reactions have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.

Bronchospasm

Bronchospasm (an acute reduction of ≥ 15% in FEV_1) is a complication associated with nebulised therapies. Bronchospasm has been reported after Cayston administration (see section 4.8). Patients should use a bronchodilator before each dose of Cayston. If a case of bronchospasm is suspected to be part of an allergic reaction appropriate measures should be taken (see "allergic reactions" paragraph above).

Haemoptysis

Inhalation of nebulised solutions may induce a cough reflex. The use of Cayston in paediatric CF patients has been associated with haemoptysis during treatment cycles and could have aggravated underlying conditions. Administration of Cayston in CF patients with active haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Other precautions

Efficacy has not been established in patients with FEV_1 > 75% predicted. Patients with *Burkholderia cepacia* isolated from sputum within the previous 2 years were excluded from the clinical studies.

Aztreonam for injection must not be used in the Altera or other nebulisers. Aztreonam for injection has not been formulated for inhalation, and contains arginine, a substance known to cause pulmonary inflammation.

Resistance to aztreonam, other antibiotics and treatment-emergent microorganisms

The development of antibiotic-resistant *P. aeruginosa* and superinfection with other pathogens represent potential risks associated with antibiotic therapy. Development of resistance during inhaled aztreonam therapy could limit treatment options during acute exacerbations. A decrease in *P. aeruginosa* susceptibility to aztreonam and other beta-lactam antibiotics was observed in clinical studies of Cayston. In a 24-week active-controlled clinical study of Cayston therapy, increases were observed in the MIC_{90} for all *P. aeruginosa* isolates as well as in the percentages of patients with *P. aeruginosa* resistant (MIC above the parenteral breakpoint) to aztreonam, to at least 1 beta-lactam antibiotic, and to all 6 beta-lactam antibiotics tested (see section 5.1). However, decreased *P. aeruginosa* susceptibility was not predictive of clinical efficacy of Cayston during the study. Among patients with multidrug-resistant *P. aeruginosa*, improvements in respiratory symptoms and pulmonary function were observed following treatment with Cayston. The emergence of parenteral *P. aeruginosa* resistance to aztreonam or other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics.

An increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), *Aspergillus* and *Candida* species was observed over time in patients treated with several Cayston treatment courses. An association between persistent isolation of MRSA and worse clinical outcome has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. However, no evidence of any drug interactions with aztreonam were identified from clinical studies in which Cayston was taken concomitantly with bronchodilators, dornase alfa, pancreatic enzymes, azithromycin, tobramycin, oral steroids (less than 10 mg daily/20 mg every other day) and inhaled steroids.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of aztreonam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Systemic concentration of aztreonam following inhaled administration of Cayston is low compared to a standard dose of aztreonam for injection (approximately 1% of the concentration resulting from a dose of 500 mg aztreonam for injection).

Cayston should not be used during pregnancy unless the clinical condition of the woman requires treatment with aztreonam.

Breast-feeding

Following administration of aztreonam for injection, aztreonam is excreted in human milk at very low concentrations. Systemic concentration of aztreonam following inhaled administration of Cayston is approximately 1% of the concentration resulting from a standard dose of aztreonam for injection. Therefore, and because of low oral absorption, aztreonam exposure in breast-fed infants due to mothers receiving Cayston is likely to be extremely low.

Cayston can be used during breast-feeding.

Fertility

Non-clinical data for aztreonam for injection about fertility do not indicate any adverse effects.

4.7 Effects on ability to drive and use machines

Cayston has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on experience in four Phase 3 clinical studies involving CF patients with chronic *P. aeruginosa* infection and post-marketing spontaneous reporting.
In the two Phase 3 placebo-controlled clinical studies where patients received Cayston for 28 days, the most frequently occurring adverse reactions to Cayston were cough (58%), nasal congestion (18%), wheezing (15%), pharyngolaryngeal pain (13.0%), pyrexia (12%) and dyspnoea (10%).

An acute reduction of $\geq$ 15% in FEV_1 is a complication associated with nebulised therapies, including Cayston (see section 4.4).

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment from clinical study and post-marketing experience are listed below by body system organ class and frequency.

Frequencies are defined as follows: very common ($\geq$ 1/10), common ($\geq$ 1/100 to < 1/10) and uncommon ($\geq$ 1/1000 to < 1/100).

Respiratory, thoracic and mediastinal disorders:	
Very common:	cough, nasal congestion, wheezing, pharyngolaryngeal pain, dyspnoea
Common:	bronchospasm[1], chest discomfort, rhinorrhoea, haemoptysis[1]
Skin and subcutaneous tissue disorders:	
Common:	rash[1]
Musculoskeletal and connective tissue disorders:	
Common:	arthralgia
Uncommon:	joint swelling
General disorders and administration site conditions:	
Very common:	pyrexia
Investigations:	
Common:	lung function test decreased[1]

[1] See section c. Description of selected adverse reactions

Description of selected adverse reactions

Bronchospasm

Nebulised therapies, including Cayston, may be associated with bronchospasm (an acute reduction of $\geq$ 15% in FEV_1). Refer to section 4.4.

Haemoptysis

Inhalation of nebulised solutions may induce a cough reflex which could aggravate underlying conditions (see section 4.4).

Allergic reactions

Rash has been reported with the use of Cayston and may be indicative of an allergic reaction to aztreonam (see section 4.4).

Lung function test decreased

Lung function test decreased has been reported with use of Cayston, but was not associated with a sustained decrease in FEV_1 (see section 5.1).

The following rare and severe adverse reactions have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.

Paediatric population

A total of 137 paediatric patients aged 6 to 17 years with chronic *P. aeruginosa* infection and FEV_1 $\leq$ 75% predicted have received Cayston in Phase 2 and Phase 3 clinical studies (6-12 years, n = 35; 13-17 years, n = 102).

Pyrexia was observed at a higher incidence rate in paediatric patients aged 6 to 17 years compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Adverse reactions specifically associated with overdose of Cayston have not been identified. Since the plasma concentration of aztreonam following administration of Cayston (75 mg) is approximately 0.6 µg/ml, compared to serum levels of 54 µg/ml following administration of aztreonam for injection (500 mg), no safety issues associated with aztreonam overdose are anticipated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other beta-lactam antibacterials,
ATC code: J01DF01

Mechanism of action

Aztreonam exhibits activity *in vitro* against gram-negative aerobic pathogens, including *P. aeruginosa*. Aztreonam binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis, followed by filamentation and cell lysis.

Mechanisms of resistance

Loss of susceptibility to aztreonam in CF patients with *P. aeruginosa* occurs either through selection of strains with mutations located on the chromosome or rarely through acquisition of plasmid/integron mediated genes.

Known mechanisms of resistance to aztreonam mediated by mutation of chromosomal genes include: hyperexpression of the Class C beta-lactamase AmpC and up-regulation of the efflux pump MexAB-OprM. The known mechanism of resistance to aztreonam mediated by acquisition of genes involves acquisition of extended spectrum beta-lactam enzymes (ESBLs) that hydrolyse the four-member, nitrogen-containing ring of aztreonam.

ESBLs from Class A, B and D beta-lactamases may have activity against aztreonam. Class A beta-lactamases reported to hydrolyse aztreonam include the VEB type (primarily Southeast Asia), PER type (Turkey), and GES and IBC types (France, Greece, and S. Africa). There are rare reports of organisms with metallo-beta-lactamases (MBLs), Class B, that are resistant to aztreonam, VIM-5 (*K. pneumoniae* and *P. aeruginosa* - Turkey), VIM-6 (*P. putida* - Singapore) and VIM-7 (*P. aeruginosa* - United States), however, it is possible that these organisms were expressing multiple resistance mechanisms and thus a MBL was not responsible for the observed resistance to aztreonam. There are rare reports of Class D beta-lactamases from clinical isolates of *P. aeruginosa*, OXA-11 (Turkey) and OXA-45 (United States) that hydrolyse aztreonam.

Microbiology

A single sputum sample from a CF patient may contain multiple isolates of *P. aeruginosa* and each isolate may have a different level of *in vitro* susceptibility to aztreonam. The *in vitro* antimicrobial susceptibility test methods used for parenteral aztreonam therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from CF patients.

In the Phase 3 placebo-controlled studies of Cayston, local aztreonam concentrations generally exceeded aztreonam MIC values for *P. aeruginosa*, regardless of the level of *P. aeruginosa* susceptibility.

Treatment with up to nine 28-day courses of 75 mg 3 times a day Cayston therapy resulted in clinically important improvements in respiratory symptoms, pulmonary function, and sputum *P. aeruginosa* CFU density; no increases in *P. aeruginosa* MIC_{50} (± 2 dilution change) were observed,

whereas MIC_{90} increased intermittently to 4 times the initial MIC. In a 24-week active-controlled study of Cayston therapy, no increases in *P. aeruginosa* MIC_{50} (± 2 dilution change) were observed, whereas MIC_{90} increased to 4 times the initial MIC. At the end of the study, the percentage of patients with aztreonam MIC for *P. aeruginosa* above the parenteral breakpoint (> 8 µg/ml) increased from 34% at baseline to 49%, the percentage of patients with *P. aeruginosa* resistant to at least 1 beta-lactam antibiotic increased from 56% at baseline to 67%, and the percentage of patients with *P. aeruginosa* resistant to all 6 beta-lactam antibiotics tested increased from 13% at baseline to 18%. There is a risk that *P. aeruginosa* isolates may develop resistance to aztreonam or other beta-lactam antibiotics in patients treated with Cayston. The emergence of parenteral *P. aeruginosa* resistance to aztreonam and other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics. However, similar improvements in lung function were seen after treatment with Cayston among patients with aztreonam susceptible or resistant *P. aeruginosa* isolates.

In studies of up to nine 28-day courses of Cayston therapy, no increases of clinical significance were observed in the treatment-emergent isolation of other gram-negative bacterial respiratory pathogens (*Burkholderia* species, *Stenotrophomonas maltophilia* and *Alcaligenes* species). During the 6-month randomised phase of study GS-US-205-0110, treatment-emergent isolation of MSSA and MRSA was observed more commonly among aztreonam-treated patients than Tobramycin Nebuliser Solution (TNS)-treated patients. The majority of the treatment-emergent isolations were intermittent. Treatment-emergent persistent isolation (defined as absent at screening/baseline then present at 3 or more subsequent consecutive visits) of MSSA occurred in 6% of aztreonam-treated patients compared to 3% of TNS-treated patients. Treatment-emergent intermittent isolation of MRSA occurred in 7% of aztreonam-treated patients compared to 1% of TNS-treated patients and treatment-emergent persistent isolation of MRSA occurred in 3% of aztreonam-treated patients compared to no TNS-treated patients. An association between persistent isolation of MRSA and more severe disease and increased mortality has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.

Clinical efficacy and safety

Cayston was compared to TNS over three 28-day courses of treatment in a randomised, active-controlled, multicenter study (GS-US-205-0110). Patients participating in this study in Europe who completed at least 1 course of Cayston or TNS during the randomised phase could subsequently receive up to three 28-day courses of Cayston in an open-label extension phase. Entry criteria included CF, $FEV_1 \leq 75\%$ predicted, stable pulmonary disease, a recent positive sputum culture for *P. aeruginosa*, and previous treatment with aerosolised antibiotics without demonstration of drug intolerance.

Cayston was evaluated over a period of 28-days of treatment (one course) in two randomised, double-blind, placebo-controlled, multicentre studies (CP-AI-005 and CP-AI-007). Patients participating in these studies could subsequently receive multiple courses of Cayston in an open-label follow-on study (CP-AI-006). Entry criteria included CF, baseline FEV_1 between 25% and 75% predicted, and chronic *P. aeruginosa* lung infection.

Overall, 539 patients (78% adults) were treated in these studies. Studies were conducted using the Altera Nebuliser System to administer Cayston.

GS-US-205-0110

In GS-US-205-0110, 268 patients with CF and chronic *P. aeruginosa* lung infection were randomised and received Cayston (n = 136) or TNS (n = 132). Fifty-nine paediatric patients aged 6 to 17 years were included in the study. Patients were randomised in a 1:1 ratio to receive either aztreonam (75 mg) administered by inhalation 3 times a day or TNS (300 mg) administered 2 times a day. Treatments were administered for three cycles of 28 days on therapy followed by 28 days off therapy. The co-primary endpoints were non-inferiority of Cayston to TNS in relative change from baseline to Day 28 in FEV_1 % predicted and superiority of Cayston to TNS in actual change from baseline in

FEV_1 % predicted across 3 treatment courses (the average of the actual change in FEV_1 % predicted observed at the end of each treatment course).

The adjusted mean percent change from baseline to Day 28 in FEV_1 % predicted was 8.35 and 0.55 in the Cayston and TNS groups, respectively (treatment difference: 7.80; p = 0.0001; 95% CI: 3.86, 11.73). The adjusted mean actual change from baseline in FEV_1 % predicted across 3 treatment courses was 2.05 and -0.66 in the Cayston and TNS groups, respectively (treatment difference: 2.70; p = 0.0023; 95% CI: 0.98, 4.43). Patients treated with aztreonamexperienced a longer time to need for i.v. antipseudomonal antibiotics related to respiratory events compared to TNS-treated patients (p = 0.0025). The Kaplan-Meier estimates for this event rate at week 24 were 36% in aztreonam-treated patients and 54% in TNS-treated patients. Additionally, aztreonam-treated patients had fewer hospitalisations due to respiratory events (40 *versus* 58, p = 0.044) and fewer respiratory events requiring the use of i.v. or inhaled antipseudomonal antibiotics (84 *versus* 121, p = 0.004) than TNS-treated patients. Aztreonam-treated patients also demonstrated larger mean improvements in CFQ-R respiratory symptoms scores compared to TNS-treated patients across 3 treatment courses (6.30 *versus* 2.17, p = 0.019).

In the limited subgroup of patients who received inhaled tobramycin for less than 84 days in the previous 12 months (n = 40), lung function improvements at Day 28 and across three 28-day treatment courses were numerically smaller among aztreonam-treated patients than TNS-treated patients.

CP-AI-007

CP-AI-007 enrolled 164 adult (predominantly) and paediatric patients randomised in a 1:1 ratio comparing Cayston 75 mg (80 patients) or placebo (84 patients) administered 3 times a day for 28 days (one course). Patients were required to have been off antipseudomonal antibiotics for at least 28 days before treatment with study drug.

Pulmonary function and respiratory symptoms significantly improved from baseline to Day 28 in patients treated with one course of Cayston.

CP-AI-005

CP-AI-005 enrolled 246 adult (predominantly) and paediatric patients. All patients were treated with Tobramycin Nebuliser Solution (TNS) 300 mg, 2 times a day in the four weeks immediately prior to receiving Cayston or placebo either 2 or 3 times a day for 28 days. Patients continued on their baseline medications, including macrolide antibiotics. Patients were randomised in a 2:2:1:1 ratio to be treated with aztreonam 75 mg 2 or 3 times a day or volume-matched placebo 2 or 3 times a day for 28 days immediately following the 28-day lead-in course of open-label TNS.

Aztreonamtherapy resulted in significant improvements in pulmonary function and respiratory symptoms at Day 28 in the 66 patients treated with one course Cayston 75 mg 3 times a day.

CP-AI-006

CP-AI-006 was an open-label follow-on study to CP-AI-005 and CP-AI-007 evaluating the safety of repeated exposure to aztreonamand the effect on disease-related endpoints over multiple 28-day courses. Patients received Cayston at the same frequency (2 or 3 times a day) as they took Cayston or placebo in the randomised studies. Patients continued on their baseline medications and whenever indicated additional antibiotics were used in the majority of patients to treat exacerbations. Each 28-day course of Cayston was followed by a 28-day off drug period. Over nine 28-day courses of therapy, measures of pulmonary function (FEV_1), CFQ-R respiratory symptoms scores, and *P. aeruginosa* sputum density showed a trend to improvement while the patients were on treatment compared with off treatment. However, due to the uncontrolled nature of the study and concomitant medications no conclusion can be drawn on the sustainability of the observed short term benefit over subsequent courses of treatment.

Paediatric population

A total of 137 paediatric patients aged 6 to 17 years with chronic *P. aeruginosa* infection and FEV_1 ≤ 75% predicted have received Cayston in Phase 2 and Phase 3 clinical studies. Paediatric patients had clinical improvements with aztreonamas determined by an increase in FEV_1, improvement in CFQ-R respiratory symptoms scores and decline in *P. aeruginosa* sputum density. Cayston is indicated for use in paediatric patients aged 6 years and older with repeated cycles of 28 days on therapy followed by 28 days off Cayston therapy based on the above clinical experience.

In a Phase 2 open-label study (GS-US-205-0162), 105 paediatric patients aged 3 months to < 18 years (24 patients aged 3 months to < 2 years; 25 patients aged 2 to < 6 years; 56 patients aged 6 to < 18 years) with CF and documented initial/new onset *P. aeruginosa* infection/colonisation received Cayston 3 times a day for a single course of 28 days.

Of the 101 patients, all having a positive cultures for *P. aeruginosa* within 30 days of study enrolment, of whom 56 (55.4%) were free of *P. aeruginosa* at baseline who completed a 28-day treatment course 89.1% (n = 90) were free of *P. aeruginosa* at the end of treatment (Day 28) and 75.2% (n = 76) were free of *P. aeruginosa* 1 month after the end of treatment (Day 56). A total of 79 patients who completed a 28-day treatment course and who did not receive an additional antipseudomonal antibiotic during the treatment period were evaluable 6 months after the end of treatment; of these, 58.2% (n = 46) remained free of *P. aeruginosa* throughout this time period.

The European Medicines Agency has deferred the obligation to submit the results of studies with Cayston in one or more subsets of the paediatric population in cystic fibrosis patients with *Pseudomonas aeruginosa* pulmonary infection/colonisation (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Sputum concentrations

Individual patients' sputum aztreonam concentrations exhibited considerable variability. For the combined Phase 3 placebo-controlled studies, ten minutes following a single dose of 75 mg inhaled aztreonamon Days 0, 14, and 28, the mean sputum concentrations in 195 patients with CF were 726 µg/g, 711 µg/g, and 715 µg/g, respectively, indicating no increased accumulation of aztreonam following repeated dosing.

Plasma concentrations

Individual patients' plasma aztreonam concentrations exhibited considerable variability.

One hour following a single dose of 75 mg inhaled aztreonam (at approximately peak plasma concentration), the mean plasma level in patients with CF was 0.59 µg/ml. Mean peak plasma levels at Days 0, 14, and 28 of a course with 75 mg inhaled aztreonam 3 times a day were 0.55 µg/ml, 0.67 µg/ml, and 0.65 µg/ml, respectively, indicating no systemic accumulation of aztreonam following 3 times a day dosing. In contrast, the serum concentration of aztreonam following administration of aztreonam for injection (500 mg) is approximately 54 µg/ml.

Plasma aztreonam concentrations in paediatric patients aged 3 months to < 6 years are comparable to those observed for children > 6 years, adolescents and adults.

Distribution

The protein binding of aztreonam in plasma is approximately 77% at clinically relevant plasma concentrations.

Metabolism

Aztreonam is not extensively metabolised. The principal metabolite (SQ26,992) is inactive and is formed by opening of the beta-lactam ring due to hydrolysis. Recovery data indicate that about 10% of the dose is excreted as this metabolite.

Elimination

The elimination half-life of aztreonam from serum is approximately 2.1 hours for inhalation administration, similar to what has been reported for aztreonam for injection. Approximately 10% of the total inhaled aztreonamdose is excreted in the urine as unchanged drug, as compared to 60-65% following intravenous administration of aztreonam for injection. Systemically absorbed aztreonam is eliminated about equally by active tubular secretion and glomerular filtration.

Pharmacokinetics in special populations

Age and gender

There was no clinically relevant effect of age or sex on the pharmacokinetics of aztreonam.

Renal and hepatic impairment

Pharmacokinetic studies have not been performed in patients with renal or hepatic impairment.

Pharmacokinetic properties for aztreonam for injection

Peak levels of aztreonam are achieved at about one hour after i.m. administration. After identical single i.m. or i.v. doses, the serum concentrations are comparable at 1 hour (1.5 hours from the start of i.v. infusion), with similar slopes of serum concentrations thereafter. The serum half-life of aztreonam averaged 1.7 hours in subjects with normal renal function, independent of the dose and route. In healthy subjects 60-70% of a single i.m. or i.v. dose was recovered in the urine by 8 hours, and urinary excretion was essentially complete by 12 hours.

Paediatric population

The Phase 2 and 3 placebo-controlled, registrational studies permitted comparison of plasma concentrations 1 hour post dose of Cayston by age (6 to 12 years, 13 to 17 years, and ≥ 18 years). Data from these studies revealed minimal differences in mean plasma aztreonam concentrations between age groups in patients receiving Cayston 3 times a day.

Pooled sputum concentration data from the Phase 2 and 3 registrational studies revealed some evidence of lower mean sputum concentrations in patients aged 13 to 17 years following one dose of Cayston 3 times a day. However, all mean sputum concentration values were associated with relatively large standard deviations.

5.3 Preclinical safety data

A 104-week rat inhalation toxicology study to assess the carcinogenic potential of ascending doses of aztreonamdemonstrated no drug-related increase in malignant tumours.

Genotoxicity (Chromosomal aberration and mouse lymphoma mutation assay) studies with aztreonam were negative.

Fertility, teratology, perinatal and postnatal studies were conducted with aztreonam for i.v. injection in rats at daily doses up to 750 mg/kg without adverse effects. The survival rate during the lactation period was slightly reduced in the offspring of rats that received the highest dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

L-Lysine

Solvent

Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Powder vial: 4 years.

Solvent: 3 years.

After reconstitution, immediate use of Cayston is recommended. If not used immediately, the reconstituted solution must be stored at 2°C - 8°C and used within 8 hours. In-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Powder vial and solvent ampoule: Store in a refrigerator (2°C - 8°C). May be stored outside a refrigerator but below 25°C for up to 28 days.

For storage conditions of the reconstitued medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder vial: Type I amber glass vial with siliconised grey rubber stopper and aluminium tear off overseal with or without a blue cap.

Solvent: 1 ml low density polyethylene ampoule.

Each 28-day pack of Cayston contains 84 vials of lyophilised aztreonam and 88 solvent ampoules. The four additional solvent ampoules are provided in case of spillage.

The following pack sizes are available:

- 28-day pack of Cayston
- Pack containing one 28-day pack of Cayston plus one Altera Nebuliser Handset

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution

Cayston should only be reconstituted with the solvent provided. Following reconstitution, Cayston is a clear, colourless to slightly coloured solution.

It is recommended that Cayston be administered immediately after reconstitution with solvent. Cayston should not be reconstituted until a dose is ready to be administered. One glass vial containing Cayston is opened by tearing and flipping up the blue cap or lifting up the metal flap, the metal ring is removed by carefully pulling the flap (tweezers or small pliers may be used to remove the metal ring if necessary) and the grey rubber stopper removed. The liquid is squeezed out of one solvent ampoule into the glass vial. The vial is then gently swirled until contents have completely dissolved. The reconstituted Cayston is then poured into the Altera Nebuliser Handset and the dose administered.

Cayston is administered by inhalation over a 2 to 3 minute period, using a Cayston specific Altera Nebuliser Handset and Altera Aerosol Head connected to an eBase Controller or an eFlow rapid Control Unit. Cayston should not be used with any other type of handset or aerosol head. Cayston should not be mixed with any other medicinal products in the Altera Nebuliser Handset. Do not put other medicinal products in the Altera Nebuliser Handset.

Do not reconstitute or mix Cayston with any other solvent or medicinal product. Do not reconstitute more than one dose at a time. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd
Granta Park
Abington
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/001
EU/1/09/543/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2009
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEXE 2:

Meropenen SmPC

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Meropenem 1 g powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for solution for injection or infusion contains 1141.56 mg meropenem trihydrate equivalent to 1 g anhydrous meropenem.

Excipients with known effect: Each vial contains 208 mg sodium carbonate approximately 4.0 mmol of sodium (approximately 90 mg).

Each ml of reconstituted solution contains 50 mg Meropenem. For the full list

of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion. A White to pale

yellow crystalline powder.

pH of the product after reconstitution is 7.3 to 8.3

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age (see sections 4.4 and 5.1):

- Severe pneumonia, including hospital and ventilator-associated pneumonia.
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Meropenem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The tables below provide general recommendations for dosing.

The dose of meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.

A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as nosocomial infections due to Pseudomonas aeruginosa or Acinetobacter spp.) or very severe infections.

Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).

Adults and adolescents

Infection	**Dose to be administered every 8 hours**
Severe pneumonia including hospital and ventilator-associated pneumonia.	500 mg or 1 g
Broncho-pulmonary infections in cystic fibrosis	2 g
Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g
Intra- and post-partum infections	500 mg or 1 g
Complicated skin and soft tissue infections	500 mg or 1 g

Acute bacterial meningitis	2 g
Management of febrile neutropenic patients	1 g

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see section 6.2, 6.3 and 6.6).

Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.

Renal impairment

The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below. There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

Creatinine clearance (ml/min)	**Dose** (based on "unit" dose range of 500 mg or 1 g or 2 g, see table above)	**Frequency**
26-50	one unit dose	every 12 hours
10-25	half of one unit dose	every 12 hours
<10	half of one unit dose	every 24 hours

Meropenem is cleared by haemodialysis and haemofiltration. The required dose should be administered after completion of the haemodialysis cycle.

There are no established dose recommendations for patients receiving peritoneal dialysis.

Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment (see section 4.4).

Dose in elderly patients

No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 ml/min.

Paediatric population

Children under 3 months of age

The safety and efficacy of meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regimen (see section 5.2).

Children from 3 months to 11 years of age and up to 50 kg body weight

The recommended dose regimens are shown in the table below:

Infection	**Dose to be administered every 8 hours**
Severe pneumonia including hospital and ventilator-associated pneumonia	10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg

Children over 50 kg body weight

The adult dose should be administered.

There is no experience in children with renal impairment.

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see sections 6.2, 6.3, and 6.6). Alternatively, meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.

Meropenem is a white to pale yellow crystalline powder for solution for injection or infusion in vial.

Product after reconstitution is clear colourless to yellow solution.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to any other carbapenem antibacterial agent.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of betalactam antibacterial agent (e.g. penicillins or cephalosporins).

4.4 Special warnings and precautions for use

The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp resistance

Resistance to penems of Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp. varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

Hypersensitivity reactions

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported (see sections 4.3 and 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

Antibiotic-associated colitis

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti- bacterial agents, including meropenem, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of meropenem (see section 4.8). Discontinuation of therapy with meropenem and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Seizures

Seizures have infrequently been reported during treatment with carbapenems, including meropenem (see section 4.8).

Hepatic function monitoring

Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) (see section 4.8).

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem. There is no dose adjustment necessary (see section 4.2).

Direct antiglobulin test (Coombs test) seroconversion

A positive direct or indirect Coombs test may develop during treatment with meropenem.

Concomitant use with valproic acid/sodium valproate/valpromide

The concomitant use of meropenem and valproic acid/sodium valproate is not recommended (see section 4.5).

Paediatric population

Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

Meropenem contains sodium.

This medicinal product contains approximately 4.0 mmol (or 90 mg) of sodium per 1 g dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No specific medicinal product interaction studies other than probenecid were conducted.

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with meropenem.

The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid with carbapenem agents is not considered to be manageable and therefore should be avoided (see section 4.4).

Oral anti-coagulants

Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalized ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after coadministration of antibiotics with an oral anti-coagulant agent.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of meropenem in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Breastfeeding

It is unknown whether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that headache, paraesthesia and convulsions have been reported for meropenem.

4.8 Undesirable effects

In a review of 4,872 patients with 5,026 meropenem treatment exposures, meropenem-related adverse reactions most frequently reported were diarrhoea (2.3 %), rash (1.4 %), nausea/vomiting (1.4 %) and injection site inflammation (1.1 %). The most commonly reported meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and increased hepatic enzymes (1.5-4.3 %).

Adverse reactions listed in the table with a frequency of “not known” were not observed in the 2,367 patients who were included in pre-authorisation clinical studies

with intravenous and intramuscular meropenem but have been reported during the post-marketing period.

Tabulated risk of adverse reactions

In the table below all adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

System Organ Class	Frequency	Event
Infections and infestations	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	thrombocythaemia
	Uncommon	eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia
Immune system disorders	Uncommon	angioedema, anaphylaxis (see sections 4.3 and 4.4)
Nervous system disorders	Common	headache
	Uncommon	paraesthesiae
	Rare	convulsions (see section 4.4)
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea, abdominal pain
	Uncommon	antibiotic-associated colitis (see section 4.4)
Hepatobiliary disorders	Common	transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased.
	Uncommon	blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	rash, pruritis
	Uncommon	urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme.
Renal and urinary disorders	Uncommon	blood creatinine increased, blood urea increased
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	Thrombophlebitis, pain at the injection site

Paediatric population

Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described in section 4.2. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile described in section 4.8, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered.

In individuals with normal renal function, rapid renal elimination will occur.

Haemodialysis will remove meropenem and its metabolite.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01DH02

Mechanism of action

Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gramnegative bacteria through binding to penicillin-binding proteins (PBPs).

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

Similar to other beta-lactam antibacterial agents, the time that meropenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy. In preclinical models meropenem demonstrated activity when plasma concentrations exceeded the MIC of the infecting organisms for approximately 40 % of the dosing interval. This target has not been established clinically.

Mechanism of resistance

Bacterial resistance to meropenem may result from: (1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) reduced affinity of the target PBPs (3) increased expression of efflux pump components, and (4) production of beta-lactamases that can hydrolyse carbapenems.

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in the European Union.

There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).

Breakpoints

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.

EUCAST clinical MIC breakpoints for meropenem (2015-01-01, v5)

Organism	**Susceptible (S) (mg/l)**	**Resistant (R) (mg/l)**
Enterobacteriaceae	≤ 2	> 8
Pseudomonas spp.	≤ 2	> 8
Acinetobacter spp.	≤ 2	> 8
Streptococcus groups A, B, C, G	note 6	note 6
Streptococcus pneumoniae[1]	≤ 2	> 2
Viridans group *streptococci*[2]	≤ 2	> 2
Enterococcus spp	--	--
Staphylococcus spp.	note 3	note 3
Haemophilus influenzae[1,2] *and Moraxella catarrhalis*[2]	≤ 2	> 2
Neisseria meningitidis[2,4]	≤ 0.25	> 0.25
Gram-positive anaerobes except *Clostridium difficile*	≤ 2	> 8
Gram-negative anaerobes	≤ 2	> 8
Listeria monocytogenes	≤ 0.25	> 0.25
Non-species related breakpoints[5]	≤ 2	> 8

[1] Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25 mg/l (Susceptible) and 1 mg/l (Resistant).

[2] Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.

[3] Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.

[4] Breakpoints relate to meningitis only.

[5] Non-species related breakpoints have been determined mainly from PK/PD data and are independent of the MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Non species related breakpoints are based on the following dosages: EUCAST breakpoints apply to meropenem 1000 mg

x 3 daily administered intravenously over 30 minutes as the lowest dose. 2 g x 3 daily was taken into consideration for severe infections and in setting the I/R breakpoint.

[6] The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

Isolates may be reported as R without prior testing.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The following table of pathogens listed is derived from clinical experience and therapeutic guidelines.

Commonly susceptible species

Gram-positive aerobes

Enterococcus faecalis[$]

Staphylococcus aureus (methicillin-susceptible)£

Staphylococcus species (methicillin-susceptible) including Staphylococcus epidermidis

Streptococcus agalactiae (Group B)

Streptococcus milleri group (S. anginosus, S. constellatus, and S. intermedius)

Streptococcus pneumoniae

Streptococcus pyogenes (Group A)

Gram-negative aerobes

Citrobacter freudii

Citrobacter koseri

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Morganella morganii

Neisseria meningitides

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Gram-positive anaerobes

Clostridium perfringens

Peptoniphilus asaccharolyticus

Peptostreptococcus species (including P. micros, P anaerobius, P. magnus)

Gram-negative anaerobes

Bacteroides caccae

Bacteroides fragilis group

Prevotella bivia

Prevotella disiens

Species for which acquired resistance may be a problem

Gram-positive aerobes

Enterococcus faecium$†

Gram-negative aerobes

Acinetobacter species

Burkholderia cepacia

Pseudomonas aeruginosa

Inherently resistant organisms

Gram-negative aerobes

Stenotrophomonas maltophilia

Legionella species

Other micro-organisms

Chlamydophila pneumoniae

Chlamydophila psittaci

Coxiella burnetii

Mycoplasma pneumonia

$ Species that show natural intermediate susceptibility

£ All methicillin-resistant staphylococci are resistant to meropenem

† Resistance rate≥ 50% in one or more EU countries.

Glanders and melioidosis: Use of meropenem in humans is based on *in vitro B.mallei* and

B. pseudomallei susceptibility data and on limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of glanders and melioidosis.

5.2 Pharmacokinetic properties

In healthy subjects the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 l/kg (11-27 l) and the mean clearance is 287 ml/min at 250 mg falling to 205 ml/min at 2 g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean Cmax values of approximately 23, 49 and 115 μg/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur. After infusion over 5 minutes Cmax values are 52 and 112 μg.h/ml.

A study of 12 patients administered meropenem 1000 mg 8 hourly post-surgically for intra-abdominal infections showed a comparable Cmax and half-life to normal subjects but a greater volume of distribution 27 l.

Distribution

The average plasma protein binding of meropenem was approximately 2 % and was independent of concentration. After rapid administration (5 minutes or less) the pharmacokinetics are biexponential but this is much less evident after 30 minutes infusion. Meropenem has been shown to penetrate well into several body fluids and tissues: including lung, bronchial secretions, bile, cerebrospinal fluid, gynaecological tissues, skin, fascia, muscle, and peritoneal exudates.

Metabolism

Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. In vitro meropenem shows reduced susceptibility to hydrolysis by human dehydropeptidase-I (DHP-I) compared to imipenem and there is no requirement to co-administer a DHP-I inhibitor.

Elimination

Meropenem is primarily excreted unchanged by the kidneys; approximately 70 % (50 –75 %) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Faecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

Renal insufficiency

Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 ml/min), 5 fold in severe impairment (CrCL 4-23 ml/min) and 10 fold in haemodialysis patients (CrCL <2 ml/min) when compared to healthy subjects (CrCL >80 ml/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment (see section 4.2).

Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients.

Hepatic insufficiency

A study in patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of meropenem after repeated doses.

Adult patients

Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.

Paediatrics

The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed C_{max} values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months $t_{1/2}$ 1.6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (6-12 years), 6.2 ml/min/kg (2- 5 years), 5.3 ml/min/kg (6-23 months) and 4.3 ml/min/kg (2-5 months). Approximately 60 % of the dose is excreted in urine over 12 hours as meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter- individual variability.

The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 %T>MIC for *P. aeruginosa* in 95 % of pre-term and 91 % of full term neonates.

Elderly

Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose

adjustment is required in elderly patients, except in cases of moderate to severe renal impairment (see section 4.2).

5.3 Preclinical safety data

Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above after a single administration and above and in monkeys at 500 mg/kg in a 7-day study.

Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000 mg/kg.

The IV LD50 of meropenem in rodents is greater than 2000 mg/kg.

In repeat dose studies of up to 6 months duration only minor effects were seen including a decrease in red cell parameters in dogs.

There was no evidence of mutagenic potential in a conventional test battery and no evidence of reproductive toxicity including teratogenic potential in studies in rats up to 750 mg/kg and in monkeys up to 360 mg/kg.

There was increased evidence of abortions at 500 mg/kg in a preliminary study in monkeys.

There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies.

The sole metabolite of meropenem had a similar profile of toxicity in animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate,anhydrous

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After reconstitution:

Intravenous bolus injection administration

A solution for bolus injection is prepared by dissolving the drug product meropenem in sterile water for injection to a final concentration of 50 mg/ml.

Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated up to 3 hours at controlled room temperature (15-25°C) or up to 8 hours under refrigerated conditions (2-8°C). From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.

If not used immediately in-use storage times and conditions are the responsibility of the user.

Intravenous infusion administration

A solution for infusion is prepared by dissolving the drug product meropenem in either 0.9% sodium chloride solution for infusion or 5% glucose (dextrose) solution for infusion to a final concentration of 1 to 20 mg/ml.

Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 6 hours at controlled room temperature (15-25°C) or upto12 hours under refrigerated conditions (2-8°C). In this case, the prepared solution if stored under refrigeration (i.e. 2-8°C) should be used within 1 hour after it has left the refrigerator.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

Reconstituted solution of meropenem in 5% glucose (dextrose) solution should be used immediately, i.e. within 30 minutes following reconstitution.

Do not freeze the reconstituted solution.

6.4 Special precautions for storage

The medicinal product does not require any special storage condition.

6.5 Nature and contents of container

1349.56 mg powder in a 40ml Type-I, tubular, clear glass vial with stopper (bromobutyl rubber with aluminum seals having white colour polypropylene discs).

The medicinal product is supplied in pack sizes of 1 or 10 vials.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Injection

Meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection.

Infusion

For intravenous infusion meropenem vial may be directly constituted with 0.9% sodium chloride or 5% glucose (dextrose) solutions for infusion.

Each vial is for single use only.

Standard aseptic techniques should be used for solution preparation and administration.

The solution should be shaken before use. The solutions should be inspected visually for particles and discolouration prior to administration. Only clear colourless to yellow solution, free from particles should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited

Ares Block, Odyssey Business Park

West End Road

Ruislip HA4 6QD

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0444

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/11/2015

10 DATE OF REVISION OF THE TEXT

24/11/2015

ANNEXE 3:

Piperacillin/Tazobactam SmPC

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tazocin 4 g / 0.5 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains piperacillin (as sodium salt) equivalent to 4 g and tazobactam (as sodium salt) equivalent to 0.5 g.

Each vial of Tazocin 4 g / 0.5 g contains 11.35 mmol (261 mg) of sodium. Excipients: For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion. White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tazocin is indicated for the treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

Adults and adolescents

- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including diabetic foot infections)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Tazocin may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Children 2 to 12 years of age

- Complicated intra-abdominal infections

Tazocin may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The dose and frequency of Tazocin depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients

Infections

The usual dose is 4 g piperacillin / 0.5 g tazobactam given every 8 hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

Treatment frequency	**Tazocin 4 g / 0.5 g**
Every 6 hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

Patients with renal impairment

The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	**Tazocin (recommended dose)**
> 40	No dose adjustment necessary
20-40	Maximum dose suggested: 4 g / 0.5 g every 8 hours
< 20	Maximum dose suggested: 4 g / 0.5 g every 12 hours

For patients on haemodialysis, one additional dose of piperacillin / tazobactam 2 g / 0.25 g should be administered following each dialysis period, because haemodialysis removes 30%-50% of piperacillin in 4 hours.

Patients with hepatic impairment
No dose adjustment is necessary (see section 5.2).

Elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)

Infections

The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

Dose per weight and treatment frequency	**Indication / condition**
80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours	Neutropenic children with fever suspected to be due to bacterial infections*
100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours	Complicated intra-abdominal infections*

* Not to exceed the maximum 4 g / 0.5 g per dose over 30 minutes.

Patients with renal impairment

The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	Tazocin (recommended dose)
> 50	No dose adjustment needed.
≤ 50	70 mg piperacillin / 8.75 mg tazobactam / kg every 8 hours.

For children on haemodialysis, one additional dose of 40 mg piperacillin / 5 mg tazobactam / kg should be administered following each dialysis period.

Use in children aged below 2 years

The safety and efficacy of Tazocin in children 0- 2 years of age has not been established.

No data from controlled clinical studies are available.

Treatment duration

The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Method of administration

Tazocin 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients listed in section 6.1.

History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

4.4 Special warnings and precautions for use

The selection of piperacillin / tazobactam to treat an individual patient should take into account the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.

Before initiating therapy with Tazocin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam agents (e.g. cephalosporin, monobactam or carbapenem) and other allergens. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid

[including shock]) reactions have been reported in patients receiving therapy with penicillins, including piperacillin / tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures.

Tazocin may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis (see section 4.8). If patients develop a skin rash they should be monitored closely and Tazocin discontinued if lesions progress.
Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Tazocin, should be discontinued.

Therapy with Tazocin may result in the emergence of resistant organisms, which might cause super-infections.

Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics. These reactions sometimes have been associated with abnormalities of coagulation tests, such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

Leukopenia and neutropenia may occur, especially during prolonged therapy; therefore, periodic assessment of haematopoietic function should be performed.

As with treatment with other penicillins, neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function.

Each vial of Tazocin 2 g / 0.25 g contains 5.67 mmol (130 mg) of sodium and Tazocin 4 g / 0.5 g contains 11.35 mmol (261 mg) of sodium. This should be taken into consideration for patients who are on a controlled sodium diet.

Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.

4.5 Interaction with other medicinal products and other forms of interaction

Non-depolarising muscle relaxants

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanisms of action, it is expected that the neuromuscular blockade

produced by any of the non-depolarising muscle relaxants could be prolonged in the presence of piperacillin.

Oral anticoagulants

During simultaneous administration of heparin, oral anticoagulants and other substances that may affect the blood coagulation system including thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.

Methotrexate

Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid substance toxicity.
Probenecid

As with other penicillins, concurrent administration of probenecid and piperacillin / tazobactam produces a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either substances are unaffected.

Aminoglycosides

Piperacillin, either alone or with tazobactam, did not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.
The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Vancomycin

No pharmacokinetic interactions have been noted between piperacillin / tazobactam and vancomycin.

However, a limited number of retrospective studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin / tazobactam and vancomycin as compared to vancomycin alone.

Effects on laboratory tests

Non-enzymatic methods of measuring urinary glucose may lead to false-positive results, as with other penicillins. Therefore, enzymatic urinary glucose measurement is required under Tazocin therapy.

A number of chemical urine protein measurement methods may lead to false-positive results. Protein measurement with dip sticks is not affected.

The direct Coombs test may be positive.

Bio-Rad Laboratories *Platelia Aspergillus* EIA tests may lead to false-positive results for patients receiving Tazocin. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories *Platelia Aspergillus* EIA test have been reported.

Positive test results for the assays listed above in patients receiving Tazocin should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or a limited amount of data from the use of Tazocin in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

Piperacillin and tazobactam cross the placenta. Piperacillin / tazobactam should only be used during pregnancy if clearly indicated, i.e. only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding
Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Fertility
A fertility study in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most commonly reported adverse reaction is diarrhoea (occurring in 1 patient out of 10).

Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis occur in 1 to 10 patients in 10,000. The frequencies for pancytopenia, anaphylactic shock and Stevens-Johnson syndrome cannot be estimated from the currently available data.

In the following table, adverse reactions are listed by system organ class and MedDRA-preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Frequency not known (cannot be estimated from available data)
Infections and infestations		candidiasis*			
Blood and lymphatic system disorders		thrombocytopenia, anaemia*, Coombs direct test positive, activated partial thromboplastin time prolonged	leukopenia, prothrombin time prolonged	agranulocytosis, epistaxis	pancytopenia*, neutropenia, haemolytic anaemia*, purpura, bleeding time prolonged, thrombocytosis*, eosinophilia*
Immune system disorders					anaphylactoid reaction*, anaphylactic reaction*, anaphylactoid shock*, anaphylactic shock*, hypersensitivity*
Metabolism and nutrition disorders		blood albumin decreased, protein total decreased	hypokalaemia, blood glucose decreased		
Nervous system disorders		headache, insomnia			
Vascular disorders			hypotension, thrombophlebitis, phlebitis, flushing		
Gastrointestinal disorders	diarrhoea	abdominal pain, vomiting, nausea, constipation, dyspepsia		pseudo-membranous colitis, stomatitis	
Hepatobiliary disorders		aspartate aminotransferase increased alanine aminotransferase increased, blood alkaline phosphatase increased	blood bilirubin increased		hepatitis*, jaundice, gamma-glutamyltransferase increased

Skin and subcutaneous tissue disorders		rash, pruritus	erythema multiforme*, urticaria, rash maculopapular*	toxic epidermal necrolysis*	Stevens-Johnson syndrome*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis bullous
Musculoskeletal and connective tissue disorders			arthralgia, myalgia		
Renal and urinary disorders		blood creatinine increased, blood urea increased			renal failure, tubulointerstitial nephritis*
General disorders and administration site conditions		pyrexia, injection site reaction	chills		

*ADR identified post marketing

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms
There have been post-marketing reports of overdose with piperacillin / tazobactam. The majority of those events experienced, including nausea, vomiting, and diarrhoea, have also been reported with the usual recommended dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment
In the event of an overdose, piperacillin / tazobactam treatment should be discontinued. No specific antidote is known.

Treatment should be supportive and symptomatic according to the patient's clinical presentation.

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins incl. beta-lactamase inhibitors; ATC code: J01C R05

Mechanism of action

Piperacillin, a broad-spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell-wall synthesis.

Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillins and cephalosporinsbut it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Phamacokinetic / Pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major pharmacodynamic determinant of efficacy for piperacillin.

Mechanism of resistance

The two main mechanisms of resistance to piperacillin / tazobactam are:

- Inactivation of the piperacillin component by those beta-lactamases that are not inhibited by tazobactam: beta-lactamases in the Molecular class B, C and D. In addition, tazobactam does not provide protection against extended-spectrum beta-lactamases (ESBLs) in the Molecular class A and D enzyme groups.

- Alteration of penicillin-binding proteins (PBPs), which results in the reduction of the affinity of piperacillin for the molecular target in bacteria.

Additionally, alterations in bacterial membrane permeability, as well as expression of multi-drug efflux pumps, may cause or contribute to bacterial resistance to piperacillin / tazobactam, especially in Gram-negative bacteria.

Breakpoints

EUCAST Clinical MIC Breakpoints for Piperacillin / Tazobactam (2009-12-02, v 1). For Susceptibility Testing Purposes, the Concentration of Tazobactam is Fixed at 4 mg/l

Pathogen	Species-related breakpoints (S≤/R>)
Enterobacteriaceae	8/16
Pseudomonas	16/16
Gram-negative and Gram-positive anaerobes	8/16
Non-species related breakpoints	4/16

The susceptibility of *streptococci* is inferred from the penicillin susceptibility.
The susceptibility of *staphylococci* is inferred from the oxacillin susceptibility.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to piperacillin / tazobactam susceptibility
COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Listeria monocytogenes* *Staphylococcus aureus,* methicillin-susceptible[£] *Staphylococcus* species, *coagulase negative,* methicillin-susceptible *Streptococcus pyogenes* *Group B streptococci*
Aerobic Gram-negative micro-organisms *Citrobacter koseri* *Haemophilus influenza* *Moraxella catarrhalis* *Proteus mirabilis*
Anaerobic Gram-positive micro-organisms *Clostridium* species *Eubacterium* species *Peptostreptococcus* species
Anaerobic Gram-negative micro-organisms *Bacteroides fragilis* group

Groupings of relevant species according to piperacillin / tazobactam susceptibility
COMMONLY SUSCEPTIBLE SPECIES
Fusobacterium species *Porphyromonas* species *Prevotella* species

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecium*[$,+] *Streptococcus pneumonia* *Streptococcus viridans group*
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*[$] *Burkholderia cepacia* *Citrobacter freundii* *Enterobacter* species *Escherichia coli* *Klebsiella pneumonia* *Morganella morganii* *Proteus vulgaris* *Providencia ssp.* *Pseudomonas aeruginosa* *Serratia* species
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Corynebacterium jeikeium*
Aerobic Gram-negative micro-organisms *Legionella* species *Stenotrophomonas maltophilia*[+,$]
Other microorganisms *Chlamydophilia pneumonia* *Mycoplasma pneumonia*
[$] Species showing natural intermediate susceptibility. [+] Species for which high-resistance rates (more than 50%) have been observed in one or more areas/countries/regions within the EU. [£] All methicillin-resistant staphylococci are resistant to piperacillin / tazobactam.

5.2 Pharmacokinetic properties

Absorption

The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 µg/ml and 34 µg/ml respectively.

Distribution

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin / tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gallbladder, lung, bile, and bone. Mean tissue concentrations are generally 50 to 100% of those in plasma. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Biotransformation

Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite that has been found to be microbiologically inactive.

Elimination

Piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion.

Piperacillin is excreted rapidly as unchanged substance, with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80% of the administered dose appearing as unchanged substance and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Following single or multiple doses of piperacillin / tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.

There are no significant changes in piperacillin pharmacokinetics due to tazobactam. Piperacillin appears to slightly reduce the clearance of tazobactam.

Special populations

The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects.

The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase in half-life is two-fold and four-fold for

piperacillin and tazobactam, respectively, at creatinine clearance below 20 ml/min compared to patients with normal renal function.

Haemodialysis removes 30% to 50% of piperacillin / tazobactam, with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 18% of the tazobactam dose removed as the tazobactam metabolite.

Paediatric population
In a population PK analysis, estimated clearance for 9 month-old to 12 year-old patients was comparable to adults, with a population mean (SE) value of 5.64 (0.34) ml/min/kg. The piperacillin clearance estimate is 80% of this value for paediatric patients 2-9 months of age. The population mean (SE) for piperacillin volume of distribution is 0.243 (0.011) l/kg and is independent of age.

Elderly patients
The mean half-life for piperacillin and tazobactam were 32% and 55% longer, respectively, in the elderly compared with younger subjects. This difference may be due to age-related changes in creatinine clearance.

Race
No difference in piperacillin or tazobactam pharmacokinetics was observed between Asian (n=9) and Caucasian (n=9) healthy volunteers who received single 4 g / 0.5 g doses.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity studies have not been conducted with piperacillin / tazobactam.

A fertility and general reproduction study in rats using intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs, concurrent with maternal toxicity. Fertility of the F1 generation and embryonic development of F2 generation were not impaired.

Teratogenicity studies using intravenous administration of tazobactam or the combination piperacillin / tazobactam in mice and rats resulted in slight reductions in rat fetal weights at maternally toxic doses but did not show teratogenic effects.

Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam in the rat.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Edetate disodium (EDTA)
Citric acid monohydrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever Tazocin is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

Tazocin should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Due to chemical instability, Tazocin should not be used in solutions containing only sodium bicarbonate.

Tazocin should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

Unopened vial: 3 years

Reconstituted solution in vial

Chemical and physical in-use stability has been demonstrated for up to 12 hours when stored in a refrigerator at 2-8°C, when reconstituted with one of the compatible solvents for reconstitution (see section 6.6).

Diluted infusion solution

After reconstitution, chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 24 hours at 25°C and for 48 hours when stored in a refrigerator at 2-8°C, when reconstituted using one of the

compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).

From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2-8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vials: Do not store above 25°C.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

70 ml Type I glass vial with a bromo-butyl rubber stopper and flip-off seal.

Pack sizes: 1, 5, 10, 12 or 25 vials per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Intravenous use

Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved. When swirled constantly, reconstitution generally occurs within 5 to 10 minutes (for details on handling, please see below).

Content of vial	Volume of solvent* to be added to vial
2 g / 0.25 g (2 g piperacillin and 0.25 g tazobactam)	10 ml
4 g / 0.5 g (4 g piperacillin and 0.5 g tazobactam)	20 ml

* Compatible solvents for reconstitution:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Sterile water for injections(1)
- Glucose 5%

(1) Maximum recommended volume of sterile water for injection per dose is 50 ml.

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:
- 0.9% (9 mg/ml) sodium chloride solution for injection
- Glucose 5%
- Dextran 6% in 0.9% (9 mg/ml) sodium chloride
- Lactated Ringers injection
- Hartmann's solution
- Ringer's acetate
- Ringer's acetate/malate

Co-administration with aminoglycosides

Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, Tazocin and the aminoglycoside are recommended for separate administration. Tazocin and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.

In circumstances where co-administration is recommended, Tazocin is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	Tazocin Dose	Tazocin diluent volume (ml)	Aminoglycoside concentration range* (mg/ml)	Acceptable diluents
Amikacin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	1.75 – 7.5	0.9% sodium chloride or 5% glucose
Gentamicin	2 g / 0.25 g 4 g / 0.5 g	50, 100, 150	0.7 – 3.32	0.9% sodium chloride or 5% glucose

* The dose of aminoglycoside should be based on patient weight, status of infection (serious or life-threatening) and renal function (creatinine clearance).

Compatibility of Tazocin with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dose of Tazocin listed in the above table have been established as compatible for co-administration via Y-site infusion. Simultaneous co-administration via Y-site in any manner other than listed above may result in inactivation of the aminoglycoside by Tazocin.

See section 6.2 for incompatibilities.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1294

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/07/2011

10 DATE OF REVISION OF THE TEXT

08/07/2016

ANNEXE 4:

Ceftazidime SmPC

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ceftazidime 3 g Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3495 mg ceftazidime pentahydrate corresponding to 3 g ceftazidime

Excipient with known effect:
153.6 mg (6.68 mmol) of sodium/vial of Powder for solution for injection or infusion

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion
The powder is white or off-white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftazidime is indicated for the treatment of the infections listed below in adults and children including neonates (from birth).

- Nosocomial pneumonia
- Broncho-pulmonary infections in cystic fibrosis
- Bacterial meningitis
- Chronic suppurative otitis media
- Malignant otitis externa
- Complicated urinary tract infections
- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections
- Bone and joint infections

- Peritonitis associated with dialysis in patients on CAPD.

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Ceftazidime may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Ceftazidime may be used in the peri-operative prophylaxis of urinary tract infections for patients undergoing trans-urethral resection of the prostate (TURP).

The selection of ceftazidime should take into account its antibacterial spectrum, which is mainly restricted to aerobic Gram negative bacteria (see sections 4.4 and 5.1).

Ceftazidime should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum of activity.

Consideration should be given to official guidances on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Routes of administration:
1 g Powder for solution for injection or infusion:
Intravenous use,
Intramuscular use (in exceptional clinical situations)

Only for 2 g and 3 g Powder for solution for injection or infusion:
Intravenous use

Posology

Table 1: Adults and children ≥ 40 kg

Intermittent Administration	
Infection	Dose to be administered
Broncho-pulmonary infections in cystic fibrosis	100 to 150 mg/kg/day every 8 h, maximum 9 g per day[1]
Febrile neutropenia	2 g every 8 h
Nosocomial pneumonia	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	1-2 g every 8 h

Complicated skin and soft tissue infections	
Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	
Complicated urinary tract infections	1-2 g every 8 h or 12 h
Peri-operative prophylaxis for transuretheral resection of prostate (TURP)	1 g at induction of anaesthesia, and a second dose at catheter removal
Chronic suppurative otitis media	1 g to 2 g every 8 h
Malignant otitis externa	
Continuous Infusion	
Infection	Dose to be administered
Febrile neutropenia	Loading dose of 2 g followed by a continuous infusion of 4 to 6 g every 24 h[1]
Nosocomial pneumonia	
Broncho-pulmonary infections in cystic fibrosis	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	
Complicated skin and soft tissue infections	
Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	
[1] In adults with normal renal function 9 g/day has been used without adverse effects. *When associated with, or suspected to be associated with, any of the infections listed in section 4.1.	

Table 2: Children < 40 kg

Infants and toddlers> 2 months and children < 40 kg	
Intermittent Administration	
Infection	Usual dose
Complicated urinary tract infections	100-150 mg/kg/day in three divided doses, maximum 6 g/day
Chronic suppurative otitis media	
Malignant otitis externa	
Neutropenic children	150 mg/kg/day in three divided doses, maximum 6 g/day
Broncho-pulmonary infections in cystic fibrosis	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	100-150 mg/kg/day in three divided doses, maximum 6 g/day
Complicated skin and soft tissue infections	

Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	
Continuous Infusion	
Infection	Usual dose
Febrile neutropenia	Loading dose of 60-100 mg/kg followed by a continuous infusion 100-200 mg/kg/day, maximum 6 g/day
Nosocomial pneumonia	
Broncho-pulmonary infections in cystic fibrosis	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	
Complicated skin and soft tissue infections	
Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	
Neonates and infants ≤ 2 months	
Intermittent Administration	
Infection	Usual dose
Most infections	25-60 mg/kg/day in two divided doses[1]
[1] In neonates and infants ≤ 2 months, the serum half-life of ceftazidime can be three to four times that in adults. * Where associated with, or suspected to be associated with, any of the infections listed in section 4.1.	

Paediatric population
The safety and efficacy of Ceftazidime administered as continuous infusion to neonates and infants ≤ 2 months has not been established.

Elderly
In view of the age related reduced clearance of ceftazidime in elderly patients, the daily dose should not normally exceed 3 g in those over 80 years of age.

Hepatic impairment
Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment. There are no study data in patients with severe hepatic impairment (see also section 5.2). Close clinical monitoring for safety and efficacy is advised.

Renal impairment

Ceftazidime is excreted unchanged by the kidneys. Therefore, in patients with impaired renal function, the dosage should be reduced (see also section 4.4).

An initial loading dose of 1 g should be given. Maintenance doses should be based on creatinine clearance:

Table 3: Recommended maintenance doses of Ceftazidime in renal impairment – intermittent infusion

Adults and children ≥40 kg

Creatinine clearance (ml/min)	Approx. serum creatinine µmol/l (mg/dl)	Recommended unit dose of Ceftazidim Stragen (g)	Frequency of dosing (hourly)
50-31	150-200 (1.7-2.3)	1	12
30-16	200-350 (2.3-4.0)	1	24
15-6	350-500 (4.0-5.6)	0.5	24
<5	>500 (>5.6)	0.5	48

In patients with severe infections the unit dose should be increased by 50% or the dosing frequency increased.
In children the creatinine clearance should be adjusted for body surface area or lean body mass.

Children < 40 kg

Creatinine clearance ml/min**	Approx. serum creatinine* µmol/l(mg/dl)	Recommended individual dose mg/kg body weight	Frequency of dosing (hourly)
50 – 31	150 - 200 (1.7 - 2.3)	25	12
30 – 16	200 - 350 (2.3 - 4.0)	25	24
15 – 6	350 - 500 (4.0 - 5.6)	12.5	24
< 5	> 500 (> 5.6)	12.5	48
* The serum creatinine values are guideline values that may not indicate exactly the same degree of reduction for all patients with reduced renal function. ** Estimated based on body surface area, or measured.			

Close clinical monitoring for safety and efficacy is advised.

Table 4: Recommended maintenance doses of Ceftazidime in renal impairment – continuous infusion

Adults and children ≥ 40 kg

Creatinine clearance (ml/min)	Approx. serum creatinine µmol/l (mg/dl)	Usual dose
50-31	150-200 (1.7-2.3)	Loading dose of 2 g followed by 1 g to 3 g /24 hours
30-16	200-350 (2.3-4.0)	Loading dose of 2 g followed by 1 g/24 hours
≤15	>350 (>4.0)	Not evaluated

Caution is advised in dose selection. Close clinical monitoring for safety and efficacy is advised.

Children < 40 kg

The safety and effectiveness of Ceftazidime administered as continuous infusion in renally impaired children < 40 kg has not been established. Close clinical monitoring for safety and efficacy is advised.

If continuous infusion is used in children with renal impairment, the creatinine clearance should be adjusted for body surface area or lean body mass.

Haemodialysis

The serum half-life during haemodialysis ranges from 3 to 5 h.

Following each haemodialysis period, the maintenance dose of ceftazidime recommended in the below table should be repeated.

Peritoneal dialysis

Ceftazidime may be used in peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD).
In addition to intravenous use, ceftazidime can be incorporated into the dialysis fluid (usually 125 to 250 mg for 2 litres of dialysis solution).

For patients in renal failure on continuous arterio-venous haemodialysis or high-flux haemofiltration in intensive therapy units:1g daily either as a single dose or in divided doses. For low-flux haemofiltration, follow the dose recommended under renal impairment.

For patients on veno-venous haemofiltration and veno-venous haemodialysis, follow the dosage recommendations in the tables below.

Table 5: Continuous veno-venous haemofiltration dose guidelines

Residual renal	Maintenance dose (mg) for an ultrafiltration rate

function (creatinine clearance ml/min)	(ml/min) of [1]:			
	5	16.7	33.3	50
0	250	250	500	500
5	250	250	500	500
10	250	500	500	750
15	250	500	500	750
20	500	500	500	750
[1] Maintenance dose to be administered every 12 h				

Table 6: Continuous veno-venous haemodialysis dose guidelines

Residual renal function (creatinine clearance ml/min)	Maintenance dose (mg) for a dialysate in flow rate of [1]:					
	1.0 litre/h			2.0 litres/h		
	Ultra filtration rate (litre/h)			Ultra filtration rate (litre/h)		
	0.5	1.0	2.0	0.5	1.0	2.0
0	500	500	500	500	500	750
5	500	500	750	500	500	750
10	500	500	750	500	750	1000
15	500	750	750	750	750	1000
20	750	750	1000	750	750	1000
[1] Maintenance dose to be administered every 12 h						

Method of administration

Ceftazidime should be administered by intravenous injection or infusion, or by deep intramuscular injection. Recommended intramuscular injection sites are the upper outer quadrant of the *gluteus maximus* or lateral part of the thigh. Ceftazidime solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids.

The standard recommended route of administration is by intravenous intermittent injection or intravenous continuous infusion. Intramuscular administration should only be considered when the intravenous route is not possible or less appropriate for the patient.

The dose depends on the severity, susceptibility, site and type of infection and on the age and renal function of the patient.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to ceftazidime, to any other cephalosporin or to any of the excipients listed in section 6.1.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (pencillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with ceftazidime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of beta-lactam agents. Caution should be used if ceftazidime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Ceftazidime has a limited spectrum of antibacterial activity. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment with ceftazidime. This particularly applies when considering the treatment of patients with bacteraemia and when treating bacterial meningitis, skin and soft tissue infections and bone and joint infections. In addition, ceftazidime is susceptible to hydrolysis by several of the extended spectrum beta lactamases (ESBLs). Therefore information on the prevalence of ESBL producing organisms should be taken into account when selecting ceftazidime for treatment.

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all anti-bacterial agents, including ceftazidime, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftazidime (see section 4.8). Discontinuation of therapy with ceftazidime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function.

Ceftazidime is eliminated via the kidneys, therefore the dose should be reduced according to the degree of renal impairment. Patients with renal impairment should be closely monitored for both safety and efficacy. Neurological sequelae have occasionally been reported when the dose has not been reduced in patients with renal impairment (see sections 4.2 and 4.8).

Prolonged use may result in the overgrowth of non-susceptible organisms (e.g. Enterococci, fungi) which may require interruption of treatment or other appropriate measures. Repeated evaluation of the patient's condition is essential.

Ceftazidime does not interfere with enzyme-based tests for glycosuria but slight interference (false-positive) may occur with copper reduction methods (Benedict's, Fehling's, Clinitest).

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

The development of a positive Coombs' test associated with the use of ceftazidime in about 5% of patients may interfere with the cross-matching of blood.

Important information about one of the ingredients of Ceftazidime:

Ceftazidime 3 g contains 153.6 mg (6.68 mmol) sodium per vial.

The sodium content has to be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been conducted with probenecid and furosemide.

Concurrent use of high doses with nephrotoxic medicinal products may adversely affect renal function (see sections 4.4).

Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of ceftazidime with chloramphenicol is proposed, the possibility of antagonism should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amounts of data from the use of ceftazidime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Ceftazidime should be prescribed to pregnant women only if the benefit outweighs the risk.

Breast-feeding

Ceftazidime is excreted in human milk in small quantities but at therapeutic doses of ceftazidime no effects on the breast-fed infant are anticipated. Ceftazidime can be used during breast-feeding.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The most common adverse reactions are eosinophilia, thrombocytosis, phlebitis or thrombophlebitis with intravenous administration, diarrhoea, transient increases in hepatic enzymes, maculopapular or urticarcial rash, pain and/or inflammation following intramuscular injection and positive Coomb's test.

Data from sponsored and un-sponsored clinical trials have been used to determine the frequency of common and uncommon undesirable effects. The frequencies assigned to all other undesirable effects were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following convention has been used for the classification of frequency:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Unknown (cannot be estimated from the available data)

Frequency / System Organ Class	Very common (≥1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 10,000)	Unknown (cannot be estimated from the available data)
Infections and infestations			Candidiasis (including vaginitis and oral thrush)			
Blood and lymphatic system disorders		Eosinophilia Thrombocytosis	Neutropenia Leucopenia Thrombocytopenia			Agranulocytosis Haemolytic anaemia Lymphocytosis
Immune system disorders						Anaphylaxis (including bronchospasm and/or hypotension)

Frequency / System Organ Class	Very common (≥1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 10,000)	Unknown (cannot be estimated from the available data)
						(see section 4.4)
Nervous system disorders			Headache Dizziness			Neurological sequelae[1] Paraesthesia
Vascular disorders		Phlebitis or thrombophlebitis with intravenous administration				
Gastrointestinal disorders		Diarrhoea	Antibacterial agent-associated diarrhoea and colitis[2] (see section 4.4) Abdominal pain Nausea Vomiting			Bad taste
Hepatobiliary disorders		Transient elevations in one or more hepatic enzymes[3]				Jaundice
Skin and subcutaneous tissue disorders		Maculopapular or urticarial rash	Pruritus			Toxic epidermal necrolysis Stevens-Johnsons syndrome Erythema multiforme Angioedema
Renal and urinary disorders			Transient elevations of blood urea, blood urea nitrogen and/or serum creatinine		Interstitial nephritis Acure reneal failure	
General disorders and administration site conditions		Pain and/or inflammation after intramuscular injection	Fever			
Investigations		Positive Coombs' test[4]				

[1] There have been reports of neurological sequelae including tremor, myoclonia, convulsions, encephalopathy, and coma in patients with renal impairment in whom the dose of Ceftazidime has not been appropriately reduced.

[2] Diarrhoea and colitis may be associated with *Clostridium difficile* and may present as pseudomembranous colitis.

[3] ALT (SGPT), AST (SOGT), LHD, GGT, alkaline phosphatase.
[4] A positive Coombs test develops in about 5% of patients and may interfere with blood cross matching.

4.9 Overdose

Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma.

Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment (see sections 4.2 and 4.4).

Serum levels of ceftazidime can be reduced by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. Third generation cephalosporins, ATC code: J01DD02

Mechanism of action
Ceftazidime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

PK/PD relationship
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftazidime for individual target species (i.e. %T>MIC).

Mechanism of Resistance
Bacterial resistance to ceftazidime may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases. Ceftazidime may be efficiently hydrolysed by extended-spectrum beta-lactamases (ESBLs), including the SHV family of ESBLs, and AmpC enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species
- reduced affinity of penicillin-binding proteins for ceftazidime
- outer membrane impermeability, which restricts access of ceftazidime to penicillin binding proteins in Gram-negative organisms
- bacterial efflux pumps.

Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Organism	Breakpoints (mg/L)		
	S	**I**	**R**
Enterobacteriaceae	≤ 1	2-4	> 4
Pseudomonas aeruginosa	≤ 8[1]	-	> 8
Non-species related breakpoints[2]	≤ 4	8	> 8

S=susceptible, I=intermediate, R=resistant.

[1] The breakpoints relate to high dose therapy (2 g x 3).

[2] Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes.

Microbiological Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ceftazidime in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive aerobes: *Streptococcus pyogenes* *Streptococcus agalactiae*
Gram-negative aerobes: *Citrobacter koseri* *Escherichia coli* *Haemophilus influenzae* *Moraxella catarrhalis* *Neisseria meningitidis* *Proteus mirabilis* *Proteus* spp. (other) *Providencia* spp.
Species for which acquired resistance may be a problem
Gram-positive aerobes: *Staphylococcus aureus* [£] *Streptococcus pneumoniae* [£££]
Gram-negative aerobes: *Acinetobacter baumannii* [£+]. *Burkholderia cepacia* *Citrobacter freundii*

Enterobacter aerogenes *Enterobacter cloacae* *Klebsiella pneumoniae* *Klebsiella* spp. (other) *Pseudomonas aeruginosa* *Serratia* spp. *Morganella morganii*
Gram-positive anaerobes: *Clostridium perfringens* *Peptococcus* spp. *Peptostreptococcus* spp.
Gram-negative anaerobes: *Fusobacterium* spp.
Inherently resistant organisms
Gram-positive aerobes: Enterococci including *Enterococcus faecalis* and *Enterococcus faecium* *Listeria* spp.
Gram-positive anaerobes: *Clostridium difficile*
Gram-negative anaerobes: *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

£ *S .aureus* that is methicillin-susceptible are considered to have inherent low susceptibility to ceftazidime. All methicillin-resistant *S. aureus* are resistant to ceftazidime.

££ *S. pneumonia* that demonstrate intermediate susceptibility or are resistant to pencillin can be expected to demonstrate at least reduced susceptibility to ceftazidime.

+ High rates of resistance have been observed in one or more areas/countries/regions within the EU.

5.2 Pharmacokinetic properties

Absorption

After intramuscular administration of 500 mg and 1 g of ceftazidime, peak plasma levels of 18 and 37 mg/l, respectively, are achieved rapidly. Five minutes after intravenous bolus injection of 500 mg, 1 g or 2 g, plasma levels are 46, 87 and 170 mg/l, respectively. The kinetics of ceftazidime are linear

within the single dose range of 0.5 to 2 g following intravenous or intramuscular dosing.

Distribution

The serum protein binding of ceftazidime is low at about 10%. Concentrations in excess of the MIC for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial, pleural and peritoneal fluids. Ceftazidime crosses the placenta readily, and is excreted in the breast milk. Penetration of the intact blood-brain barrier is poor, resulting in low levels of ceftazidime in the CSF in the absence of inflammation. However, concentrations of 4 to 20 mg/l or more are achieved in the CSF when the meninges are inflamed.

Biotransformation

Ceftazidime is not metabolised.

Elimination

After parenteral administration plasma levels decrease with a half-life of about 2 h. Ceftazidime is excreted unchanged into the urine by glomerular filtration; approximately 80 to 90% of the dose is recovered in the urine within 24 h. Less than 1% is excreted via the bile.

Special patient populations

Renal impairment

Elimination of ceftazidime is decreased in patients with impaired renal function and the dose should be reduced (see section 4.2).

Hepatic impairment

The presence of mild to moderate hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days, provided renal function was not impaired (see section 4.2).

Elderly

The reduced clearance observed in elderly patients was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life ranged from 3.5 to 4 hours following single or 7 days repeat BID dosing of 2 g IV bolus injections in elderly patients 80 years or older.

Paediatric population

The half-life of ceftazidime is prolonged in preterm and term neonates by 4.5 to 7.5 hours after doses of 25 to 30 mg/kg. However, by the age of 2 months the half-life is within the range for adults.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeat dose toxicity, genotoxicity, toxicity to reproduction. Carcinogenicity studies have not been performed with ceftazidime.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate, anhydrous (E500)

6.2 Incompatibilities

Ceftazidime should not be mixed with solutions with a pH above 7.5 for example sodium bicarbonate solution for injection. Ceftazidime and aminoglycosides should not be mixed in the solution for infusion because of the risk for precipitation.

Cannulae and catheters for intravenous use should be flushed with physiological salt-solution between administrations of Ceftazidime and vancomycin to avoid precipitation.

6.3 Shelf life

Vial before opening: 3 years.

Vial after first opening: The product should be used immediately.

After reconstitution: The product should be used immediately.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened*:* Store below 25 °C. Keep vial in the outer carton

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Nature:
Clear colourless type II. Injection vial (100 ml) closed with bromobutyl rubber closure and polypropylene flip-off aluminium cap.

Pack sizes: 10 x 1 vial.

6.6 Special precautions for disposal and other handlings

For single use only.
The constitution is to be made under aseptic conditions.
As the product dissolves, carbon dioxide is released and a positive pressure develops. Small bubbles of carbon dioxide in the constitution solution may be ignored.

Instructions for constitution

See table for addition volumes and solution concentrations, which may be useful when fractional doses are required.

Vial size		Amount of diluent to be added (ml)	Approximate concentration (mg/ml)
1 g Powder for solution for injection or infusion			
1 g	Intramuscular	3 ml	260
	Intravenous bolus	10 ml	90
	Intravenous infusion	50 ml*	20
2 g Powder for solution for injection or infusion			
2g	Intravenous bolus	10 ml	170
	Intravenous infusion	50 ml*	40
3 g Powder for solution for injection or infusion			
3 g	Intravenous bolus	15 ml	170
	Intravenous infusion	75 ml*	40

*Note: Addition should be in two stages

Solutions range in colour from light yellow to amber depending on concentration, diluent and storage conditions used. Within the stated recommendations, the product potency is not adversely affected by such colour variation.

Ceftazidime is compatible with:

- Water for injection
- Sodium chloride solution 9 mg/ml (0.9 %) solution for injection
- Glucose 50 mg/ml (5 %)
- Glucose 50 mg/ml (5 %) in 0.9% sodium chloride injection

Ceftazidime may be constituted for intramuscular use with 1% lidocaine solution for injection.

1 g, 2 g, 3 g Powder for solution for injection or infusion.

Preparation of solutions for bolus injection

1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. Remove the syringe needle.
2. Shake to dissolve: carbon dioxide is released and a clear solution will be obtained in about 1 to 2 minutes.
3. Invert the vial. With the syringe plunger fully depressed, insert the needle through the vial closure and withdraw the total volume of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution and does not enter the head space. The withdrawn solution may contain small bubbles of carbon dioxide, they may be disregarded.

These solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids.

1 g, 2 g, 3 g Powder for solution for injection or infusion
Preparation of solutions for i.v. infusion:

Prepare using a total of 50 ml (for 1g and 2g vials) and 75 ml (for 3g vials) of compatible diluent, added in TWO stages as below.

1. Introduce the syringe needle through the vial closure and inject 10 ml of the diluent for the 1 g and 2 g vials, and 15 ml for the 3 g vial
2. Withdraw the needle and shake the vial to give a clear solution.
3. Do not insert a gas relief needle until the product has dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure.
4. Add a further 40 ml of diluent for the 1 g and 2 g vials and 60 ml for the 3 g vial. Remove the vent needle.
5. Administer by intravenous infusion over 15 to 30 min. Additional pressure that may develop in the vial especially after storage should be relieved prior to administration to the patient.

NOTE: To preserve product sterility, it is important that the gas relief needle is not inserted through the vial closure before the product has dissolved.

The solution should only be used if the solution is clear and free from particles.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Stragen UK Limited

Castle Court

41 London Road

Reigate Surrey RH2 9RJ

8 MARKETING AUTHORISATION NUMBER(S)

PL 21844/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/07/2012

10 DATE OF REVISION OF THE TEXT

19/07/2012

ANNEXE 5:

Aztreonam IV SmPC

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Azactam 2g Powder for solution for Injection or infusion, vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 g aztreonam.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The treatment of the following infections caused by susceptible aerobic Gram- negative micro-organisms:

Urinary tract infections: including pyelonephritis and cystitis (initial and recurrent) and asymptomatic bacteriuria, including those due to pathogens resistant to the aminoglycosides, cephalosporins or penicillins.

Gonorrhoea: acute uncomplicated urogenital or anorectal infections due to beta-lactamase producing or non-producing strains of *N. gonorrhoeae.*

Lower respiratory tract infections: including pneumonia, bronchitis and lung infections in patients with cystic fibrosis.

Bacteraemia/septicaemia.

Meningitis caused by *Haemophilus influenzae* or *Neisseria meningitidis*. Since Azactam provides only Gram negative cover, it should not be given alone as initial blind therapy, but may be used with an antibiotic active against Gram positive organisms until the results of sensitivity tests are known.

Bone and joint infections.

Skin and soft tissue infections: including those associated with postoperative wounds, ulcers and burns.

Intra-abdominal infections: peritonitis.

Gynaecological infections: pelvic inflammatory disease, endometritis, and pelvic cellulitis.

Azactam is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces.

Bacteriological studies to determine the causative organism(s) and their sensitivity to aztreonam should be performed. Therapy may be instituted prior to receiving the results of sensitivity tests.

In patients at risk of infections due to non-susceptible pathogens, additional antibiotic therapy should be initiated concurrently with Azactam to provide broad-spectrum coverage before identification and susceptibility testing results of the causative organism(s) are known. Based on these results, appropriate antibiotic therapy should be continued.

Patients with serious *Pseudomonas* infections may benefit from concurrent use of Azactam and an aminoglycoside because of their synergistic action. If such concurrent therapy is considered in these patients, susceptibility tests should be performed *in vitro* to determine the activity in combination. The usual monitoring of serum levels and renal function during aminoglycosides therapy applies.

4.2. Posology and method of administration

Intramuscular or intravenous injection, or intravenous infusion.
Azactam is given by deep injection into a large muscle mass, such as the upper quadrant of the gluteus maximus or the lateral part of the thigh.

Adults:
The dose range of Azactam is 1 to 8 g daily in equally divided doses. The usual dose is 3 to 4 g daily. The maximum recommended dose is 8 g daily. The dosage and route of administration should be determined by the susceptibility of the causative organisms, severity of infection and the condition of the patient.

Dosage Guide: Adults (see table below)

Type of Infection[1]	Dosage	Frequency (hours)	Route
Urinary tract infections	500 mg or 1 g	8 or 12	IM or IV

Gonorrhoea / cystitis	1 g	single dose	IM
Cystic fibrosis	2 g	6 - 8	IV
Moderately severe systemic infections	1 g or 2 g	8 or 12	IM or IV
Severe systemic or life-threatening infections	2 g	6 or 8	IM or IV
Other infections either	1 g	8	IM or IV
or	2 g	12	IV

[1] Because of the serious nature of infections due to *Pseudomonas aeruginosa*, a dose of 2 g every 6 or 8 hours is recommended, at least for initial therapy in systemic infections caused by this organism.

The intravenous route is recommended for patients requiring single doses greater than 1 g, or those with bacterial septicaemia, localised parenchymal abscess (e.g. intra-abdominal abscess), peritonitis, meningitis or other severe systemic or life-threatening infections.

Elderly:
Renal status is a major determinant of dosage in the elderly; these patients in particular may have diminished renal function. Serum creatinine may not be an accurate determinant of renal status. Therefore, as with all antibiotics eliminated by the kidneys, estimates of creatinine clearance should be obtained, and appropriate dosage modifications made if necessary.

Elderly patients normally have a creatinine clearance in excess of 30 mL/min and therefore would receive the normal recommended dose. If renal function is below this level, the dosage schedule should be adjusted (see Renal Impairment).

Renal Impairment:
Prolonged serum levels of aztreonam may occur in patients with transient or persistent renal insufficiency. Therefore, after an initial usual dose, the dosage of aztreonam should be halved in patients with estimated creatinine clearances between 10 and 30 mL/min/1.73 m^2.

In patients with severe renal failure (creatinine clearance less than 10 mL/min/1.73 m^2), such as those supported by hemodialysis, the usual dose should be given initially. The maintenance dose should be one-fourth of the usual initial dose given at the usual fixed interval of 6, 8 or 12 hours. For serious or life-threatening infections, in addition to the maintenance doses, one-eighth of the initial dose should be given after each hemodialysis session.

Paediatric:
The usual dosage for patients older than one week is 30 mg/kg/dose every 6 or 8 hours. For severe infections in patients 2 years of age or older, 50 mg/kg/dose every 6 or 8 hours is recommended. The recommended dose for all patients in the treatment of infections due to *P. aeruginosa* is 50 mg/kg every six to eight hours.

The maximum daily paediatric dose should not exceed the maximum recommended dose for adults.
Dosage information is not yet available for new-borns less than 1 week old.

For instructions on dilution of the product before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Aztreonam is contraindicated in pregnancy. Aztreonam crosses the placenta and enters the foetal circulation.

4.4. Special warnings and precautions for use

Allergic reactions
Antibiotics, like other drugs, should be given with caution to any patients with a history of allergic reaction to structurally related compounds. If an allergic reaction occurs, discontinue the drug and institute supportive treatments as appropriate. Serious hypersensitivity reactions may require epinephrine and other emergency measures. Specific studies have not shown significant cross-reactivity between Azactam and antibodies to penicillins or cephalosporins. The incidence of hypersensitivity to Azactam in clinical trials has been low but caution should be exercised in patients with a history of hypersensitivity to beta-lactam antibiotics until further experience is gained.

Renal/hepatic impairment
In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

Serious blood/skin disorders
Serious blood disorders (incl. pancytopenia) and skin disorders (incl. toxic epidermal necrolysis) have been reported with the use of aztreonam. In case of serious hemogram and skin changes, it is recommended to stop aztreonam.

Convulsions
Convulsions have rarely been reported during treatment with beta-lactams, including aztreonam (see section 4.8).

Clostridium difficile associated diarrhoea
Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Azactam, and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Medication that inhibits intestinal peristalsis should not be given.

Concurrent therapy with other antimicrobial agents and Azactam is recommended as initial therapy in patients who are at risk of having an infection due to pathogens that are not susceptible to aztreonam.

As with other antibiotics, in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis, while clinical improvement is usually noted, lasting bacterial eradications may not be achieved.

Overgrowth of non-susceptible organisms
Therapy with Azactam may result in overgrowth of non-susceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken. In comparative studies, the number of patients treated for superinfections was similar to that of the control drugs used.

Prolongation of prothrombin time / increased activity of oral anticoagulants
Prolongation of prothrombin time has been reported rarely in patients receiving aztreonam. Additionally, numerous cases of increased activity of oral anticoagulants have been reported in patients receiving antibiotics, including beta-lactams. Severe infection or inflammation, and the age and general condition of the patient appear to be risk factors. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

Concomitant use with aminoglycosides
If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

Paediatric population
Data on safety and effectiveness in neonates younger than one week are limited; use in this population needs to be carefully assessed.

Arginine
Aztreonam for injection contains arginine. Studies in low birth weight infants have demonstrated that arginine administered in the aztreonam formulation may result in increases in serum arginine, insulin, and indirect bilirubin. The consequences of exposure to this amino acid during treatment of neonates have not been fully ascertained.

Interference with serological testing
A positive direct or indirect Coombs test may develop during treatment with aztreonam.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of probenecid or furosemide and aztreonam cause clinically insignificant increases in the serum levels of aztreonam.

Due to the induction of beta-lactamases, certain antibiotics (eg, cefoxitin, imipenem) have been found to cause antagonism with many beta-lactams, including aztreonam, for certain gram-negative aerobes, such as Enterobacter species and Pseudomonas species.

Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.4 and 4.8).

Single-dose pharmacokinetic studies have not shown any significant interaction between aztreonam and gentamicin, cephradine, clindamycin or metronidazole.

Unlike broad spectrum antibiotics, aztreonam produces no effects on the normal anaerobic intestinal flora. No disulfiram-like reactions with alcohol ingestion have been reported.

4.6. Fertility, pregnancy and lactation

Pregnancy
Aztreonam is contraindicated in pregnancy. Aztreonam crosses the placenta and enters the foetal circulation.

There are no adequate and well-controlled studies in pregnant women. Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times the maximum recommended human dose respectively, revealed no evidence of embryo- or fetotoxicity or teratogenicity. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Breastfeeding
Aztreonam is excreted in breast milk in concentrations that are less than 1% of those in simultaneously obtained maternal serum. Lactating mothers should refrain from breast feeding during the course of therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects

The list of undesirable effects shown below is presented by system organ class, MedDRA preferred term, and frequency. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (≥1/10,000); Not known (cannot be estimated from the available data).

System Organ Class	Frequency	MedDRA Term
Blood and lymphatic system disorders	Rare	Pancytopenia[a], thrombocytopenia, thrombocythaemias, leukocytosis, neutropenia, eosinophilia, anaemia, prothrombin time prolonged, activated partial thromboplastin time prolonged, Coombs test positive[a]

System Organ Class	Frequency	MedDRA Term
Ear and labyrinth disorders	Rare	Vertigo, tinnitus
Eye disorders	Rare	Diplopia
Gastrointestinal disorders	Rare Not known	Gastro intestinal haemorrhage, pseudomembranous colitis[a], breath odour Abdominal pains, mouth ulceration, nausea, vomiting, diarrhoea, altered taste
General disorders and administration site conditions	Rare Not known	Chest pain, pyrexia, asthenia, malaise Injection site discomfort, weakness, sweating, muscle aches, fever, transient increases in serum creatinine
Hepato-biliary disorders	Rare Not known	Hepatitis, jaundice Transaminases increased*, blood alkaline phosphatase increased*
Infections and infestations	Rare	Vaginitis, vaginal candidiasis
Immune system disorders	Not known	Anaphylactic reaction
Investigations	Rare	Electrocardiogram change
Musculoskeletal, connective tissue and bone disorders	Rare	Myalgia
Nervous system disorders	Rare Not known	Convulsions[a], paraesthesia, dizziness, headache Dysgeusia
Psychiatric disorders	Rare	Confusional state, insomnia
Renal and urinary disorders	Uncommon	Blood creatinine increased
Reproductive system and breast disorders	Rare	Breast tenderness
Respiratory, thoracic and mediastinal disorders	Rare Not known	Wheezing, dyspnoea, sneezing, nasal congestion Bronchospasm
Skin and subcutaneous tissue disorders	Not known	Toxic epidermal necrolysis[a], angioedema, erythema multiforme, dermatitis exfoliative, hyperhidrosis, petechiae, purpura, urticaria, rash, pruritus
Vascular disorders	Rare Not known	Hypotension, haemorrhage Phlebitis, thrombophlebitis, flushing

*Usually reversing during therapy and without overt signs or symptoms of hepatobiliary dysfunction.
[a] See section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse eractions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

There have been no reported cases of overdosage. If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis. Aztreonam has been shown to be cleared from the serum by continuous arteriovenous hemofiltration.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectives for systemic use, ATC code: J01DF01

Aztreonam is a monocyclic beta-lactam antibiotic with potent bactericidal activity against a wide spectrum of Gram-negative aerobic pathogens.

Unlike the majority of beta-lactam antibiotics, it is not an inducer *in vitro* of beta-lactamase activity. Aztreonam is usually active *in vitro* against those resistant aerobic organisms whose beta-lactamases hydrolyse other antibiotics.

5.2 Pharmacokinetic Properties

Single 30-minute i.v. infusions of 0.5g, 1.0g and 2.0g in healthy volunteers produced peak serum levels of 54, 90 and 204mg/L, and single 3-minute i.v. injections of the same doses produced peak levels of 58, 125 and 242mg/L. Peak levels of aztreonam are achieved at about one hour after i.m. administration. After identical single i.m. or i.v. doses, the serum concentrations are comparable at 1 hour (1.5 hours from the start of i.v. infusion), with similar slopes of serum concentrations thereafter.

The serum half-life of aztreonam averaged 1.7 hours in subjects with normal renal function, independent of the dose and route. In healthy subjects 60-70% of a single i.m. or i.v. dose was recovered in the urine by 8 hours, and urinary excretion was essentially complete by 12 hours.

5.3 Preclinical safety data

Aztreonam was well tolerated in a comprehensive series of preclinical toxicity and safety studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine (780mg per g of aztreonam).

6.2 Incompatibilities

Azactam should not be physically mixed with any other drug, antibiotic or diluent except those listed in the Posology and Method of Administration section under reconstitution for intravenous infusion.

With intermittent infusion of Azactam and another drug via a common delivery tube, the tube should be flushed before and after delivery of Azactam with any appropriate infusion solution compatible with both drug solutions. The drugs should not be delivered simultaneously.

6.3 Shelf life

(a) Product unopened: 3 years

(b) Reconstituted product: 24 hours (2-8°C)

6.4 Special precautions for storage

(a) Product unopened:
Storage before reconstitution:
Do not store above 25°C.

(b) Reconstituted product:
Stability after reconstitution:
Store at 2-8°C for not more than 24 hours.
Discard any unused solution.

6.5 Nature and contents of container

2g glass vial: pack of 5 x 15mL

6.6. Special precautions for disposal and handling

Reconstitution
Azactam for Injection 1 g or 2 g Vial are supplied in 15 mL vials.

Upon the addition of the diluent the contents should be shaken immediately and vigorously. Vials of reconstituted Azactam are not intended for multi-dose use, and any unused solution from a single dose must be discarded. Depending on the type and amount of diluent, the pH ranges from 4.5 to 7.5, and the colour may vary from colourless to light straw-yellow, which may develop a slight pink tint on standing; however this does not affect the potency.

For intramuscular injection: For each gram of aztreonam add at least 3 mL Water for Injections Ph. Eur. or 0.9% Sodium Chloride Injection B.P. and shake well.

Single Dose Vial Size	Volume of Diluent to be Added
0.5 g	1.5 mL
1.0 g	3.0 mL

Azactam is given by deep injection into a large muscle mass, such as the upper quadrant of the gluteus maximus or the lateral part of the thigh.

For intravenous injection: To the contents of the vial add 6 to 10 mL of Water for Injections Ph. Eur. and shake well. Slowly inject directly into the vein over a period of 3 to 5 minutes.

For intravenous infusion:

Vials: For each gram of aztreonam add at least 3 mL of Water for Injections Ph. Eur. and shake well.
Dilute this initial solution with an appropriate infusion solution to a final concentration less than 2% w/v (at least 50 mL solution per gram of aztreonam). The infusion should be administered over 20-60 minutes.

Appropriate infusion solutions include:
0.9% Sodium Chloride Injection B.P.
5% Glucose Intravenous Infusion B.P.
5% or 10% Mannitol Intravenous Infusion B.P.
Sodium Lactate Intravenous Infusion B.P.
0.9%, 0.45% or 0.2% Sodium Chloride and 5% Glucose Intravenous Infusion B.P.
Compound Sodium Chloride Injection B.P.C. 1959 (Ringer's Solution for Injection)
Compound Sodium Lactate Intravenous Infusion B.P. (Hartmann's Solution for Injection).

A volume control administration set may be used to deliver the initial solution of Azactam into a compatible infusion solution being administered. With use of a Y-tube administration set, careful attention should be given to the calculated volume of Azactam solution required so that the entire dose will be infused.

Reconstitution:
Intravenous infusion solutions of Azactam for Injection prepared with 0.9% Sodium Chloride Injection B.P. or 5% Glucose Intravenous B.P., in PVC or glass containers, to which clindamycin phosphate, gentamicin sulphate, tobramycin sulphate, or cephazolin sodium have been added at concentrations usually used clinically, are stable for up to 24 hours in a refrigerator (2-8°C). Ampicillin sodium admixtures with

aztreonam in 0.9% Sodium Chloride Injection B.P. are stable for 24 hours in a refrigerator (2-8°C); stability in 5% Glucose Intravenous Infusion B.P. is eight hours under refrigeration.

If aztreonam and metronidazole are to be used together, they should be administered separately as a cherry red colour has been observed after storage of solutions containing combinations of the two products.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

E. R. Squibb & Sons Limited. Uxbridge
Business Park Sanderson Road,
Uxbridge, Middlesex, UB8 1DH

8 MARKETING AUTHORISATION NUMBER(S)

PL 00034/0252

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15th October 1986 / 22nd November 1991 / 13th August 1998

10 DATE OF REVISION OF THE TEXT

17/04/2014

ANNEXE 6:

Fosfomycin SmPC

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FOSFOMYCIN 40 mg/ml powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of reconstituted solution contains 40 mg fosfomycin.

Each bottle with 2.69 g of powder contains 2.64 g disodium fosfomycin, corresponding to 2 g fosfomycin and 0.64 g sodium, for reconstitution in 50 ml of solvent.

Each bottle with 5.38 g of powder contains 5.28 g disodium fosfomycin, corresponding to 4 g fosfomycin and 1.28 g sodium, for reconstitution in 100 ml of solvent.

Each bottle with 10.76 g of powder contains 10.56 g disodium fosfomycin, corresponding to 8 g fosfomycin and 2.56 g sodium, for reconstitution in 200 ml of solvent.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion. White to cream-coloured powder.

4.1 Therapeutic indications

Fosfomycin is indicated for the treatment of the following infections in adults and children including neonates (see section 5.1):

- Osteomyelitis
- Complicated urinary tract infections
- Nosocomial lower respiratory tract infections
- Bacterial meningitis
- Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Fosfomycin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment

of the infections listed above, or when these alternative antibacterial agents have failed to demonstrate efficacy.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.
For information regarding the combination with other antibiotics see section 4.4 and 4.5.

4.2 Posology and method of administration

The daily dose of fosfomycin is determined based on the indication, severity and site of the infection, susceptibility of the pathogen(s) to fosfomycin and the estimated creatinine clearance. In children, it is also determined by age and body weight.

Adults and adolescents ≥ 12 years of age (> 40 kg):

Fosfomycin is primarily excreted renally unchanged. The general dosage guidelines for adults with estimated creatinine clearance > 80 ml/min are as follows:

Indication	**Daily dose**
Osteomyelitis	12–24 g [a] in 2–3 divided doses
Complicated urinary tract infection	12–16 g [b] in 2–3 divided doses
Nosocomial lower respiratory tract infection	12–24 g [a] in 2–3 divided doses
Bacterial meningitis	16–24 g [a] in 3–4 divided doses

Individual doses must not exceed 8 g.

[a] The high-dose regimen in 3 divided doses should be used in severe infections expected or known to be caused by less susceptible bacteria.

[b] There are limited safety data in particular for doses in excess of 16 g/day. Special caution is advised when such doses are prescribed.

Dosage in renal insufficiency

The dose recommendations for patients with renal impairment are based on pharmacokinetic modelling and limited clinical data; safety and efficacy have not yet been evaluated in clinical trials.
It is unclear if dose reductions are necessary for patients with an estimated creatinine clearance between 40–80 ml/min. Great caution should be exercised in these cases, particularly if doses at the higher end of the recommended range are considered.

In patients with impaired renal function the dose of fosfomycin must be adjusted to the degree of renal impairment.
Dose titration should be based on creatinine clearance values. In adults, creatinine clearance may be calculated according to the following formula by Cockroft and Gault:

$$\text{Creatinine clearance } (CL_{CR}) \text{ in men [ml/min]} = \frac{(140 - \text{age [years]}) \times \text{body weight [kg]}}{72 \times \text{serum creatinine [mg/dl]}}$$

In order to calculate CL_{CR} in women, the result of this formula is multiplied by 0.85.

Dosage table for patients with impaired renal function:

$CL_{CR\ patient}$	$CL_{CR\ patient}$/ $CL_{CR\ normal}$	Daily dosage recommended [a]
40 ml/min	0.333	70% (in 2–3 divided doses)
30 ml/min	0.250	60% (in 2–3 divided doses)
20 ml/min	0.167	40% (in 2–3 divided doses)
10 ml/min	0.083	20% (in 1–2 divided doses)

[a] The dose is expressed as a proportion of the dose that would have been considered appropriate if the patient's renal function were normal.

The first dose should be increased by 100% (loading dose), but must not exceed 8 g.

Patients undergoing renal replacement therapy

Patients undergoing chronic intermittent dialysis (every 48 hours) should receive 2 g of fosfomycin at the end of each dialysis session.

During continuous veno-venous hemofiltration (post-dilution CVVHF), fosfomycin is effectively eliminated. Patients undergoing post-dilution CVVHF will not require any dose adjustment. In a study investigating 12 patients under CVVHF customary polyethylene sulfone haemofilters with a membrane surface of 1.2 m^2 and a mean ultrafiltration rate of 25 ml/min were employed. In this clinical setting, the mean values of plasma clearance and elimination half-life in plasma were 100 ml/min, and 12 h, respectively.
No clinical data exist for intravenous fosfomycin in patients undergoing pre-dilution CVVHF or other forms of renal replacement therapy.

Hepatic impairment

There are no data indicating that dose adjustment is necessary in patients with hepatic impairment.

Elderly patients

The recommended doses for adults should be used in elderly patients. Caution is advised when considering the use of doses at the higher end of the recommended range (see also recommendations on dosage for patients with impaired renal function).

Paediatric population

Dose recommendations are based on very limited data.

Neonates, infants and children < 12 years of age (< 40 kg)

The dosage of fosfomycin in children should be based on age and body weight (BW):

Age/weight	**Daily dose**
Premature neonates (age [a] < 40 weeks)	100 mg/kg BW in 2 divided doses
Neonates (age [a] 40–44 weeks)	200 mg/kg BW in 3 divided doses
Infants 1–12 months (up to 10 kg BW)	200–300 [b] mg/kg BW in 3 divided doses
Infants and children aged 1-12 years (10–40 kg BW)	200–400 [b] mg/kg BW in 3–4 divided doses

[a] Sum of gestational and postnatal age.

[b] The high-dose regimen may be considered for severe infections and or serious infections (such as meningitis), in particular when known or suspected to be caused by organisms with moderate susceptibility.

No dose recommendations can be made for children with renal impairment.

Method and duration of administration

Method of administration

Disodium fosfomycin is intended for intravenous administration. The duration of infusion should be at least 15 minutes for the 2 g pack size, at least 30 minutes for the 4 g pack size and at least 60 minutes for the 8 g pack size.

Use only clear solutions.

As damaging effects can result from inadvertent intra-arterial administration of products not specifically recommended for intra-arterial therapy, it is essential to ensure that fosfomycin is only administered into veins.

For preparation of the solution for infusion see section 6.6.

Duration of treatment

Treatment duration should take into account the type of infection, the severity of the infection as well as the patient's clinical response. Relevant therapeutic guidelines should be adhered to when deciding treatment duration.

4.3 Contraindications

- Hypersensitivity to the active substance, fosfomycin, or to any of the excipients

4.4 Special warnings and precautions for use

Consideration should be given to co-administering intravenous fosfomycin with another antibacterial agent, taking into account the remaining susceptibilities of the pathogen(s) under treatment. As it is unknown whether the development of resistance to intravenous fosfomycin is higher when it is used as a monotherapy, co-administration with other antibacterials should also be considered in order to prevent the emergence of resistance.

Caution is advised when fosfomycin is used in patients with cardiac insufficiency, hypertension, hyperaldosteronism, hypernatraemia or pulmonary oedema.

1 g fosfomycin (equivalent to 1.32 g disodium fosfomycin) contains 14 mmol (320 mg) sodium. One bottle with 2 g of fosfomycin contains 28 mmol (640 mg) sodium, one bottle with 4 g fosfomycin contains 56 mmol (1280 mg) sodium and one bottle with 8 g of fosfomycin contains 111 mmol (2560 mg) sodium.

A high sodium load associated with the use of fosfomycin may result in decreased levels of potassium in serum or plasma. A low-sodium diet is recommended during treatment. The substitution of potassium may be necessary in some cases. Serum electrolyte levels and water balance must be monitored during therapy.

Acute, potentially life-threatening hypersensitivity reactions (anaphylactic shock) may occur in very rare cases. At the first signs (including sweating, nausea, cyanosis), the infusion of fosfomycin must be immediately discontinued. The intravenous line should be left in place. Depending upon the clinical situation, appropriate emergency measures may need to be initiated.

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents including fosfomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of fosfomycin. Discontinuation of therapy with fosfomycin and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

In patients with severe renal insufficiency (creatinine clearance ≤ 40ml/min), the elimination of fosfomycin is substantially slowed. See section 4.2 for appropriate dosing of fosfomycin in renal insufficiency.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies have been performed with fosfomycin. To date, no clinically relevant pharmacological interactions between fosfomycin and other agents (drugs, stimulants or foodstuffs) have been reported.

Combination with other antibiotics

In-vitro tests have shown that the combination of fosfomycin with a β-lactam antibiotic such as penicillin, ampicillin, cefazolin or the class of carbapenems, usually shows an additive to synergistic effect. The same applies to the combination of fosfomycin with most anti-staphylococcal (linezolid, quinupristin/dalfopristin, moxifloxacin) agents in the treatment of staphylococcal infections. The combination of fosfomycin with aminoglycosides has predominantly indifferent to additive effects.

4.6 Fertility, pregnancy and lactation

Fertility

To date, in humans no reduction in fertility after therapy with fosfomycin has been reported. In male and female rats, reduced fertility was observed after the oral administration of fosfomycin at supra-therapeutic doses (see section 5.3.).

Pregnancy

For fosfomycin, no clinical data on pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Fosfomycin should therefore not be prescribed to pregnant women unless the benefit outweighs the risk.

Lactation

After the administration of fosfomycin, low quantities of fosfomycin were found in human milk. Fosfomycin should therefore not be administered during lactation, unless the benefit outweighs the risk.

4.7 Effects on ability to drive and use machines

Occasionally, even if the product is correctly administered, side effects may occur which impair the ability to drive and use machines (see also section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are gastrointestinal disturbances and injection site reactions. Other important adverse reactions include hypokalaemia and/or hypernatraemia.

Tabulated list of adverse reactions

Undesirable effects are listed by body system and frequency in accordance with the following classification:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data

System Organ Class	**Frequency Category**	**Adverse Drug Reactions**
Blood and lymphatic system disorders	Rare	Aplastic anaemia, eosinophilia
	Frequency not known	Agranulocytosis, granulocytopenia, leucopenia, pancytopenia, thrombocytopenia, neutropenia
Immune system disorders	Very rare	Anaphylactic shock (see section 4.4)
Metabolism and nutrition disorders	Uncommon	Decreased appetite, hypernatraemia and/or hypokalaemia (see section 4.4), oedema
Psychiatric disorders	Frequency not known	Confusion
Nervous system disorders	Uncommon	Dysgeusia, headache
Eye disorders	Very rare	Visual impairment
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac	Frequency	Tachycardia

System Organ Class	Frequency Category	Adverse Drug Reactions
disorders	not known	
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
	Frequency not known	Asthmatic attack
Gastrointestinal disorders	Common	Retching, stomach ache
	Uncommon	Nausea, vomiting, diarrhoea
	Frequency not known	Pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders	Uncommon	Blood alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase increased (transient)
	Very rare	Fatty liver (completely reversible after discontinuation of fosfomycin)
	Frequency not known	Hepatitis, cholestatic hepatitis, icterus
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Frequency not known	Angioedema, facial oedema, pruritus, urticaria
General disorders and administration site conditions	Common	Injection site phlebitis
	Uncommon	Fatigue

Description of selected adverse reactions
Hypokalaemia may result in diffuse symptoms such as weakness, tiredness or oedema and/or muscle twitching. Severe forms may cause hyporeflexia and cardiac arrhythmia. Hypernatraemia may be associated with hypertension and signs of fluid overload such as oedema (see section 4.4).

Paediatric population
Limited safety information is available from the paediatric population. Frequency, type and severity of adverse reactions may be expected to be similar to the adult population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance

of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

To date, no cases of accidental overdose with clinically relevant intolerances have been reported. If an overdose is believed to have taken place, the patient must be monitored (particularly for plasma/serum electrolyte levels) and treated symptomatically. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibiotics for systemic use, other antibacterials
ATC-Code: J01XX01

Mode of action

Fosfomycin exerts a bactericidal effect on proliferating pathogens by preventing the enzymatic synthesis of the bacterial cell wall. Fosfomycin inhibits the first stage of intracellular bacterial cell wall synthesis by blocking peptidoglycan synthesis.
Fosfomycin is actively transported into the bacterial cell via two different transport systems (the sn-glycerol-3-phosphate and hexose-6 transport systems).

Pharmacokinetic (PK)/pharmacodynamic (PD) relationship

Limited data indicate that fosfomycin most likely acts in a time-dependent manner.

Resistance mechanism

Main mechanism of resistance is a chromosomal mutation causing an alteration of the bacterial fosfomycin transport systems. Further resistance mechanisms, which are plasmid- or transposon-borne, cause enzymatic inactivation of fosfomycin by binding the molecule to glutathione or by cleavage of the carbon-phosphorus-bond in the fosfomycin molecule, respectively.

Cross-resistance

The mode of action of fosfomycin differs from that of all other antibiotic classes. Fosfomycin was generally found to be active *in-vitro* against clinical isolates of methicillin-resistant staphylococci, vancomycin-resistant enterococci, penicillin- and erythromycin-resistant streptococci and multiresistant *Pseudomonas*.

Antimicrobial spectrum of fosfomycin (in vitro)

The data predict only the probability of micro-organism susceptibility to fosfomycin.

For intravenous fosfomycin, the susceptibility breakpoints established by the European Committee on Antimicrobial Susceptibility Testing are as follows (EUCAST breakpoint table version 5.0, 2015)

Species	susceptible	resistant
Enterobacteriaceae	≤ 32 mg/l	> 32 mg/l
Staphylococcus spp.	≤ 32 mg/l	> 32 mg/l

The prevalence of acquired resistance of individual species may vary geographically and over time. Local information about the resistance situation is therefore necessary, particularly in order to ensure appropriate treatment of severe infections.

In-vitro activity spectrum of fosfomycin and resistance

The following table is based on the breakpoint according to EUCAST and comprises organisms relevant for the approved indications:

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus
Streptococcus pyogenes
Streptococcus pneumoniae
Aerobic Gram-negative microorganisms
Citrobacter spp.
Edwardsiella spp.
Enterobacter cancerogenus
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Neisseria spp.
Proteus mirabilis
Proteus penneri
Providencia rettgeri
Anaerobic microorganisms
Peptococcus spp.

Peptostreptococcus spp.
Species in which acquired resistance may be a problem
Gram-positive microorganisms
Enterococcus faecalis
Staphylococcus epidermidis
Gram-negative microorganisms
Enterobacter cloacae
Klebsiella pneumoniae
Proteus inconstans
Pseudomonas aeruginosa
Serratia marcescens
Inherently resistant species
Gram-negative microorganisms
Morganella morganii
Anaerobic microorganisms
Bacteroides spp.

The physiologically important apathogenic anaerobic species, *Lactobacillus* and *Bifidobacterium*, are not susceptible to fosfomycin.

5.2 Pharmacokinetic properties

Pharmacokinetics

A single intravenous infusion of 4 g and 8 g of fosfomycin in young healthy males resulted in maximum serum concentrations (C_{max}) of approx. 200 and 400 µg/ml, respectively. The serum half-life was approx. 2 hours. In elderly and/or critically ill male and female subjects, single intravenous doses of 8 g of fosfomycin resulted in mean C_{max} and half-lives in plasma of approximately 350–380 µg/ml and 3.6–3.8 h, respectively.

Distribution

The apparent volume of distribution of fosfomycin is approx. 0.30 l/kg body weight. Fosfomycin is distributed well to tissues. High concentrations are reached in eyes, bones, wound secretions, musculature, cutis, subcutis, lungs and bile. In patients with inflamed meninges, cerebrospinal fluid concentrations reach approx. 20–50% of the corresponding serum levels. Fosfomycin passes the placental barrier. Low quantities were found in human

milk (about 8 % of the serum concentrations). The plasma protein binding is negligible.

Metabolism

Fosfomycin is not metabolised by the liver and does not undergo enterohepatic circulation. No accumulation is therefore to be expected in patients with hepatic impairment.

Elimination

80–90% of the quantity of fosfomycin administered to healthy adults is eliminated renally within 10 hours after a single intravenous administration. Fosfomycin is not metabolised, i.e. the biologically active compound is eliminated. In patients with normal or mildly to moderately impaired renal function (creatinine clearance ≥ 40 ml/min), approximately 50–60% of the overall dose is excreted within the first 3–4 hours.

Linearity

Fosfomycin shows linear pharmacokinetic behaviour after intravenous infusion of therapeutically used doses.

Special populations

Very limited data are available in special populations.

Elderly

No dose adjustment is necessary based on age alone. However, renal function should be assessed and the dose should be reduced if there is evidence of renal impairment (see section 4.2).

Paediatric population

The pharmacokinetics of fosfomycin in children and adolescents aged 3–15 years as well as in term newborns with normal renal function are generally similar to those of healthy adult subjects. However, in renally healthy neonates and infants up to 12 months, the glomerular filtration rate is physiologically decreased compared to older children and adults. This is associated with a prolongation of the elimination half-life of fosfomycin in dependence on the stage of renal maturation.

Renal insufficiency

In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal insufficiency. Patients with creatinine clearance values of 40 ml/min or less require dose adjustments (see also section 4.2. “Dosage in renal insufficiency” for further details).

Hepatic insufficiency

There is no requirement for dosage adjustments in patients with hepatic insufficiency since the pharmacokinetics of fosfomycin remains unaffected in this patient group.

5.3 Preclinical safety data

Subacute and chronic toxicity

The toxicity of fosfomycin following repeated administration for up to 6 months was evaluated in rats, dogs, rabbits and monkeys. At high intra-peritoneal doses of fosfomycin (> 500 mg/kg /day), rats developed respiratory arrest, tetanic cramps, anaemia, a reduction of blood protein levels, increased serum cholesterol and reduced blood glucose. Furthermore, dogs and monkeys experienced diarrhoea due to antibiotic-related changes in the intestinal flora following intravenous administration of doses of higher than 250 mg/kg /day and 500 mg/kg /day, respectively. In the rabbit, no toxicity was observed following intravenous administration of 400 mg/kg /day for a period of 1 month.

Reproductive toxicity

Fertility

In male and female rats, following repeated administration (via a pharyngeal tube) of up to 1400 mg/kg /day reduced fertility was observed at the maximum dose tested.

Teratogenicity

Fosfomycin was administered to mice, rats and rabbits via pharyngeal tube at maximum doses of 2 x 120 mg/kg /day, 1400 mg/kg /day and 420 mg/kg /day, respectively or intravenously to mice and rabbits at 55.3 mg/kg /day, and up to 250 mg/kg /day, respectively. There was no evidence of embryotoxicity or teratogenicity.

Perinatal and postnatal toxicity

In rats, a maximum dose of 2800 mg/kg /day was administered via a pharyngeal tube. There was no evidence of foetal or peri- and postnatal toxicity.

Mutagenicity

In-vitro tests were performed to test the alkylating capacity and the mutagenic effect of fosfomycin. Fosfomycin showed no alkylating effect. In the Ames test, no mutagenic effect was seen in test strains of *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537 and TA 1538, with and without addition of rat-liver homogenate) after exposure to fosfomycin at up to 1600 µg/ml.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Succinic acid.

6.2 Incompatibilities

Although no chemical/pharmaceutical incompatibilities have been found, FOSFOMYCIN solutions should not be mixed together with other parenteral preparations with the exception of those listed in section 6.6.

6.3 Shelf life

4 years.

Chemical and physical in-use stability of the reconstituted solution that has been produced under aseptic conditions has been demonstrated for 24 hours at 25 °C if protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage of the reconstituted solution see section 6.3.

6.5 Nature and contents of container

Clear type-II glass bottles with a rubber stopper (bromobutyl rubber) and pull-off cap containing 2 g (in 100 ml bottle), 4 g (in 100 ml bottle) or 8 g (in 250 ml bottle) of FOSFOMYCIN, respectively, in packs of 10 bottles each.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation of the solution for infusion

In order to prepare the solution for infusion:

FOSFOMYCIN 2 g should be dissolved in 50 ml of Water for Injections, 5 % or 10 % Glucose Infusion.

FOSFOMYCIN 4 g should be dissolved in 100 ml of Water for Injections, 5 % or 10 % Glucose Infusion.

FOSFOMYCIN 8 g should be dissolved in 200 ml of Water for Injections, 5 % or 10 % Glucose Infusion.

A slight degree of warming occurs when the powder is dissolved.
The reconstituted solution is clear and colourless to slightly yellowish.

Displacement value

The displacement values for the reconstituted solutions are 1 ml for the 2 g pack size, 2 ml for the 4 g pack size and 4 ml for the 8 g pack size.

These volumes are equivalent to an increase of volume of 2 %. This has to be considered when preparing the final solution in case of not using the entire content of the bottle.

7 MARKETING AUTHORISATION HOLDER

InfectoPharm Arzneimittel und Consilium GmbH Von-

Humboldt-Str. 1

64646 Heppenheim

Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 15011/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/06/2013

10 DATE OF REVISION OF THE TEXT

15/02/2016

ANNEXE 7:

Colistimethate Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Colomycin Injection 2 million International Units.
Powder for solution for injection, infusion or inhalation.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 million International Units Colistimethate Sodium.
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection, infusion or inhalation.
Sterile white powder in a 10ml colourless glass vial with a lilac 'flip-off' cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Colomycin by intravenous administration is indicated in adults and children including neonates for the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options (see sections 4.2, 4.4, 4.8 and 5.1).
Colomycin by inhalation is also indicated for the management of adult and paediatric chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (see section 5.1).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

SYSTEMIC TREATMENT
The dose to be administered and the treatment duration should take into account the severity of the infection as well as the clinical response. Therapeutic guidelines should be adhered to.
The dose is expressed in international units (IU) of colistimethate sodium (CMS). A conversion table from CMS in IU to mg of CMS as well as to mg of colistin base activity (CBA) is included at the end of this section.
Posology
The following dose recommendations are made based on limited population-pharmacokinetic data in critically ill patients (see section 4.4):
Adults and adolescents
Maintenance dose 9 million IU/day in 2-3 divided doses
In patients who are critically ill, a loading dose of 9 MIU should be administered.
The most appropriate time interval to the first maintenance dose has not been established.
Modelling suggests that loading and maintenance doses of up to 12 MIU may be required in patients with good renal function in some cases. Clinical experience with such doses is however extremely limited, and safety has not been established.
The loading dose applies to patients with normal and impaired renal functions including those on renal replacement therapy.

Renal impairment
Dose adjustments in renal impairment are necessary, but pharmacokinetic data available for patients with impaired renal function is very limited.
The following dose adjustments are suggested as guidance.
Dose reductions are recommended for patients with creatinine clearance < 50 ml/min:
Twice daily dosing is recommended.

Creatinine clearance
(ml/min)
Daily dose
< 50- 30 5.5- 7.5 MIU
<30- 10 4.5- 5.5 MIU
<10 3.5 MIU
MIU = million IU
Haemodialysis and continuous haemo(dia)filtration
Colistin appears to be dialyzable through conventional haemodialysis and continuous venovenous haemo(dia)filtration (CVVHF, CVVHDF). There are extremely limited data from population PK studies from very small numbers of patients on renal replacement therapy. Firm dose recommendations cannot be made. The following regimes could be considered.
Haemodialysis
No-HD days: 2.25 MIU/day (2.2-2.3 MIU/day).
HD days: 3 MIU/day on haemodialysis days, to be given after the HD session.
Twice daily dosing is recommended.
CVVHF/ CVVHDF
As in patients with normal renal function. Three times daily dosing is recommended.
Hepatic impairment
There are no data in patients with hepatic impairment. Caution is advised when administering colistimethate sodium in these patients.
Elderly
No dose adjustments in older patients with normal renal function are considered necessary.
Paediatric population
The data supporting the dose regimen in paediatric patients are very limited. Renal maturity should be taken into consideration when selecting the dose. The dose should be based on lean body weight.
Children ≤ 40kg
75,000-150,000 IU/kg/day divided into 3 doses.
For children with a body weight above 40 kg, use of the dosing recommendation for adults should be considered.
The use of doses >150,000 IU/kg/day has been reported in children with cystic fibrosis.
There are no data regarding the use or magnitude of a loading dose in critically ill children.
No dose recommendations have been established in children with impaired renal function.
Intrathecal and intraventricular administration
Based on limited data, the following dose is recommended in adults:
Intraventricular route
125,000 IU/day
Intrathecally administered doses should not exceed those recommended for intraventricular use.
No specific dosing recommendation can be made in children for intrathecal and intraventricular routes of administration.
Method of administration
Colomycin is administered intravenously as a slow infusion over 30 – 60 minutes.
. Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus

injection of up to 2 million units in 10ml given over a minimum of 5 minutes (see section 6.6).
Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution.
For dose preparation, particularly where combination of multiple vials is needed, reconstitution of the required dose must be performed using strict aseptic technique (see section 6.6).

Dose conversion table:
In the EU, the dose of colistimethate sodium (CMS) must be prescribed and administered only as International Units (IU). The product label states the number of IU per vial.
Confusion and medication errors have occurred because of the different expressions of dose in terms of potency. The dose is expressed in the US, and other parts of the world, as milligrams of colistin base activity (mg CBA).
The following conversion table is prepared for information and the values must be considered nominal and approximate only.

CMS conversion table
Potency
IU ≈ mg CBA
≈ mass of
CMS (mg) *
12 500 0.4 1
150 000 5 12
1 000 000 34 80
4 500 000 150 360
9 000 000 300 720
* Nominal potency of the drug substance = 12,500 IU/mg
AEROSOL INHALATION
It is recommended that colistimethate sodium (CMS) should be administered under the supervision of physicians with appropriate experience in its use.
Posology
The dosage can be adjusted depending on the severity of the condition and clinical response.
Recommended dose range:
Administration via inhalation
Adults, adolescents and children ≥ 2 years
1-2 MIU two to three times per day (max 6 MIU/day)
Children < 2 years
0.5-1 MIU twice daily (max 2 MIU/ day)
Relevant clinical guidance on treatment regimens, including duration of treatment, periodicity and co-administration of other antibacterial agents should be adhered to.
Elderly
Dose adjustment is not considered necessary
Renal impairment
Dose adjustment is not considered necessary, however caution is advised in patients with renal impairment (see sections 4.4 and 5.2).
Hepatic impairment
Dose adjustment is not considered necessary.
Method of administration
For inhalation use.
Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. For special precautions for disposal and handling of reconstituted solutions, see section 6.6.
If other treatments are being taken, they should be taken in the order recommended by the

physician.
See above for Dose conversion table.

4.3 Contraindications

Hypersensitivity to colistimethate sodium (colistin) or to polymyxin B.

4.4 Special warnings and precautions for use

Consideration should be given to co-administering intravenous colistimethate sodium with another antibacterial agent whenever this is possible, taking into account the remaining susceptibilities of the pathogen(s) under treatment. As the development of resistance to intravenous colistin has been reported in particular when it is used as a monotherapy, co- administration with other antibacterial should also be considered in order to prevent the emergence of resistance.
There are limited clinical data on the efficacy and safety of intravenous colistimethate sodium. The recommended doses in all subpopulations are equally based on limited data (clinical and pharmacokinetic/ pharmacodynamics data). In particular there are limited safety data for the use of high doses (> 6MIU/day) and the use of a loading dose, and for special populations (patients with renal impairment and the paediatric population). Colistimethate sodium should only be used when other, more commonly prescribed antibiotics are not effective or not appropriate.
Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. The dose of colistimethate sodium should be adjusted according to creatinine clearance (see section 4.2). Patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin (see sections 4.5 and 4.8). Nephrotoxicity has been reported to be associated with cumulative dose and treatment duration in some studies. The benefit of prolonged treatment duration should be balanced against the potentially increased risk of renal toxicity.
Caution is advised when administering colistimethate sodium to infants < 1 year of age as renal function is not fully mature in this age group. Further, the effect of immature renal and metabolic function on the conversion of colistimethate sodium to colistin is not known.
In case of an allergic reaction, treatment with colistimethate sodium must be discontinued and appropriate measures implemented.
High serum concentrations of colistimethate sodium, which may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, have been reported to lead to neurotoxic effects such as facial paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. Monitoring should be performed for perioral paraesthesia and paraesthesia in the extremities, which are signs of overdose (see section 4.9).
Colistimethate sodium is known to reduce the presynaptic release of acetyl-choline at the neuro-muscular junction and should be used in patients with myasthenia gravis with the greatest caution and only if clearly needed.
Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnoea and neuromuscular blockade following administration of colistimethate sodium.
Colistimethate sodium should be used with extreme caution in patients with

porphyria.
Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents and may occur with colistimethate sodium. They may range from mild to life-threatening in severity. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of colistimethate sodium (see section 4.8). Discontinuation of therapy and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.
Intravenous colistimethate sodium does not cross the blood brain barrier to a clinically relevant extent. The use of intrathecal or intraventricular administration of colistimethate sodium in the treatment of meningitis was not systematically investigated in clinical trials and is supported by case reports only. Data supporting the posology are very limited. The most commonly observed adverse effect of CMS administration was aseptic meningitis (see section 4.8).
Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of beta$_2$-agonists. If troublesome, treatment should be withdrawn.

4.4 Interaction with other medicinal products and other forms of interaction

Concomitant use of intravenous colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.
Caution should be taken with concomitant use with other formulations of colistimethate sodium as there is little experience and there is a possibility of summative toxicity.
No *in vivo* interaction studies have been performed. The mechanism of conversion of colistimethate sodium to the active substance, colistin, is not characterised. The mechanism of colistin clearance, including renal handling, is equally unknown.
Colistimethate sodium or colistin did not induce the activity of any P 450 (CYP) enzyme tested (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5) in *in vitro* studies in human hepatocytes.
The potential for drug-drug interactions should be borne in mind when Colomycin is co-administered with drugs known to inhibit or induce drug metabolising enzymes or drugs known to be substrates for renal carrier mechanisms.
Due to the effects of colistin on the release of acetylcholine, non-depolarising muscle relaxants should be used with caution in patients receiving colistimethate sodium as their effects could be prolonged (see section 4.4).
Co-treatment with colistimethate sodium and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin should be undertaken with caution in patients with myasthenia gravis (see section 4.4).
Concomitant use of colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential should be avoided. These include the aminoglycoside antibiotics such as gentamicin, amikacin, netilmicin and tobramycin. There may be an increased risk of nephrotoxicity if given concomitantly with cephalosporin antibiotics.

4.6 Pregnancy and lactation
There are no adequate data from the use of colistimethate sodium in pregnant

women.
Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development (see Section 5.3 – Preclinical safety data).
Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.
Colistimethate sodium is secreted in breast milk. Colistimethate sodium should be administered to breastfeeding women only when clearly needed.

4.7 Effects on ability to drive and use machines
During parenteral treatment with colistimethate sodium neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. Patients should be warned not to drive or operate machinery if these effects occur.

4.8 Undesirable effects
Systemic treatment
The likelihood of adverse events may be related to the age, renal function and condition of the patient.
In cystic fibrosis patients neurological events have been reported in up to 27% of patients. These are generally mild and resolve during or shortly after treatment.
Neurotoxicity may be associated with overdose, failure to reduce the dose in patients with renal insufficiency and concomitant use of either neuromuscular blocking drugs or other drugs with similar neurological effects. Reducing the dose may alleviate symptoms. Effects may include apnoea, transient sensory disturbances (such as facial paraesthesia and vertigo) and, rarely, vasomotor instability, slurred speech, visual disturbances, confusion or psychosis.
Adverse effects on renal function have been reported, usually following use of higher than recommended doses in patients with normal renal function, or failure to reduce the dosage in patients with renal impairment or during concomitant use of other nephrotoxic drugs. The effects are usually reversible on discontinuation of therapy.
In cystic fibrosis patients treated within the recommended dosage limits, nephrotoxicity appears to be rare (less than 1%). In seriously ill hospitalised non-CF patients, signs of nephrotoxicity have been reported in approximately 20% of patients.
Hypersensitivity reactions including skin rash and drug fever have been reported. If these occur treatment should be withdrawn.
Local irritation at the site of injection may occur.
Inhalation treatment
Inhalation may induce coughing or bronchospasm.
Sore throat or mouth has been reported and may be due to *Candida albicans* infection or hypersensitivity. Skin rash may also indicate hypersensitivity, if

this occurs treatment should be withdrawn.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (Website: www.mhra.gov.uk/yellowcard).

4.9 Overdose
Overdose can result in neuromuscular blockade that can lead to muscular weakness, apnoea and possible respiratory arrest. Overdose can also cause acute renal failure characterised by decreased urine output and increased serum concentrations of BUN and creatinine.
There is no specific antidote, manage by supportive treatment. Measures to increase the rate of elimination of colistin e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis may be tried, but effectiveness is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, polymyxins.
ATC Code: J01XB01
Mechanism of action
Colistin is a cyclic polypeptide antibacterial agent belonging to the polymyxin group. Polymyxins work by damaging the cell membrane and the resulting physiological effects are lethal to the bacterium. Polymyxins are selective for aerobic Gramnegative bacteria that have a hydrophobic outer membrane.
Resistance
Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharide, which become substituted with ethanolamine or aminoarabinose. Naturally resistant Gram-negative bacteria, such as *Proteus mirabilis* and *Burkholderia cepacia*, show complete substitution of their lipid phosphate by ethanolamine or aminoarabinose.
Cross resistance between colistin (polymyxin E) and polymyxin B is expected. Since the mechanism of action of the polymyxins is different from that of other antibacterial agents, resistance to colistin and polymyxin by the above mechanism alone would not be expected to result in resistance to other drug classes.
PK/PD relationship
Polymyxins have been reported to have a concentration-dependent bactericidal effect on susceptible bacteria. fAUC/ MIC is considered to be correlated with clinical efficacy.
EUCAST Breakpoints Susceptible (S) Resistant (R) [a]

Acinetobacter S≤2 R>2 mg/L
Enterobacteriaceae S≤2 R>2 mg/L
Pseudomonas spp S≤4 R>4 mg/L
[a] *Breakpoints apply to dosage of 2-3 MIU x 3. A loading dose (9 MIU) may be needed.*
Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.
Commonly susceptible species
Acinetobacter baumannii
Haemophilus influenza
Klebsiella spp
Pseudomonas aeruginosa

Species for which acquired resistance may be a problem
Stenotrophomonas maltophilia
Achromobacter xylosoxidans (formerly Alcaligenes xylosoxidans)
Burkholderia cepacia and related species.
Proteus species
Providencia species
Serratia species

5.2 Pharmacokinetic properties
Absorption
The information on the pharmacokinetics of colistimethate sodium (CMS) and colistin is limited. There are indications that pharmacokinetics in critically ill patients differ from those in patients with less severe physiological derangement and from those in healthy volunteers. The following data are based on studies using HPLC to determine CMS/colistin plasma concentrations.
After infusion of colistimethate sodium the inactive pro-drug is converted to the active colistin. Peak plasma concentrations of colistin have been shown to occur with a delay of up to 7 hours after administration of colistimethate sodium in critically ill patients. Absorption from the gastrointestinal tract does not occur to any appreciable extent in the normal individual.
When given by nebulisation, variable absorption has been reported that may depend on the aerosol particle size, nebuliser system and lung status. Studies in healthy volunteers and patients with various infections have reported serum levels from nil to potentially therapeutic concentrations of 4mg/l or more. Therefore, the possibility of systemic absorption should always be borne in mind when treating patients by inhalation.
Distribution
The volume of distribution of colistin in healthy subjects is low and corresponds approximately to extracellular fluid (ECF). The volume of distribution is relevantly enlarged in critically ill subjects. Protein binding is moderate and decreases at higher

concentrations. In the absence of meningeal inflammation, penetration into the cerebrospinal fluid (CSF) is minimal, but increases in the presence of meningeal inflammation.
Both CMS and colistin display linear PK in the clinically relevant dose range.
Elimination
It is estimated that approximately 30% of colistimethate sodium is converted to colistin in healthy subjects, its clearance is dependent on creatinine clearance and as renal function decreases, a greater portion of CMS is converted to colistin. In patients with very poor renal function (creatinine clearance <30 ml/min), the extent of conversion could be as high as 60 to 70%. CMS is eliminated predominantly by the kidneys via glomerular filtration. In healthy subjects, 60% to 70% of CMS is excreted unchanged in the urine within 24 hours.
The elimination of the active colistin is incompletely characterised. Colistin undergoes extensive renal tubular reabsorption and may either be cleared non-renally or undergo renal metabolism with the potential for renal accumulation. Colistin clearance is decreased in renal impairment, possibly due to increased conversion of CMS.
Half-life of colistin in healthy subjects and those with cystic fibrosis is reported to be around 3h and 4h, respectively, with a total clearance of around 3L/h. In critically ill patients, half-life has been reported to be prolonged to around 9-18h.

5.3 Preclinical safety data

Data on potential genotoxicity are limited and carcinogenicity data for colistimethate sodium arelacking. Colistimethate sodium has been shown to induce chromosomal aberrations in human lymphocytes, in vitro. This effect may be related to a reduction in mitotic index, which was also observed. Reproductive toxicity studies in rats and mice do not indicate teratogenic properties. However, colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6 and 2.9% of fetuses respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased resorption occurred at 9.3 mg/kg.
There are no other preclinical safety data of relevance to the prescriber which are additional to safety data derived from patient exposure and already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None

6.2 Incompatibilities
Mixed infusions, injections and nebuliser solutions involving colistimethate

sodium should be avoided.

6.3 Shelf life

Before opening:

3 years.

Reconstituted solutions:

Hydrolysis of colistimethate is significantly increased when reconstituted and diluted below its critical micelle concentration of about 80,000 IU per ml.

Solutions below this concentration should be used immediately

For solutions for bolus injection or nebulisation, the chemical and physical in-use stability of reconstituted solution in the original vial, with a concentration ≥ 80,000 IU/mL, has been demonstrated for 24 hours at 2 to 8°C.

From a microbiological point of view, unless the method of opening/ reconstitution/ dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of user.

Solutions for infusion, which have been diluted beyond the original vial volume and / or with a concentration < 80,000 IU/mL should be used immediately.

For solutions for intrathecal and intraventricular administration, the reconstituted product should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the vials in the outer carton in order to protect from light.

For storage of solutions following reconstitution refer to 6.3.

6.5 Nature and contents of container

1 million IU/vial: Type I, 10 ml nominal capacity glass vial with red 'flip-off' cap supplied in cartons of ten vials.

2 million IU/vial: Type I, 10 ml nominal capacity glass vial with lilac 'flip-off' cap supplied in cartons of ten vials.

6.6 Special precautions for disposal

For bolus injection:

Reconstitute the contents of the vial with not more than 10ml water for injection or 0.9% sodium chloride.

For infusion:

The contents of the reconstituted vial may be diluted, usually with 50ml 0.9% sodium chloride.

When the intrathecal and intraventricular routes of administration are used, the volume administered should not exceed 1 ml (reconstituted concentration 125,000 IU/ml).

For inhalation by nebuliser:

Reconstitute the contents of the vial with either water for injections to produce a hypotonic solution or a 50:50 mixture of water for injections and 0.9% sodium chloride to produce an isotonic solution or with 0.9% sodium chloride to produce a hypertonic solution.

The volume of reconstitution should be according to the instructions for use of

nebuliser administration device, and is normally not more than 4ml.
The output from the nebuliser may be vented to the open air or a filter may be fitted.
Nebulisation should take place in a well ventilated room.
During reconstitution swirl gently to avoid frothing.
Solutions are for single use only and any remaining solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

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Whiddon Valley
Barnstaple
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EX32 8NS
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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

03/02/2016

Annexe 8

Letter from statistician

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

22nd September 2016

Dear Aztec Trial Team,

I am writing to comfirm my participation in and support for the execution of this trial's statistical plan as set out in the trial protocol.

I hope to be able to work closely with the trial co-ordinators in order to make a success of this interesting project.

Yours sincerely,

Matthew Shaw

Senior Clinical Information Analyst

Liverpool Heart and Chest Hospital NHS Foundation Trust