Guidance Sheet 5a: Intervention

AZTEC Azithromycin Therapy for Chronic Lung Disease | Cardiff University Prifysgol Caerdydd | Centre for Trials Research Canolfan Ymchwil Treialon

a) Storage

The AZTEC medication is an Investigational Medicinal Product (IMP) and should always be stored appropriately.

Correct Storage at Site

In the AZTEC trial there is provision for IMP being held in pharmacy and on the neonatal unit. At recruiting sites, a stock of IMP will be held on the neonatal unit and resupplied from the pharmacy as and when required. It is essential that storage requirements are observed in all cases:

- On the neonatal unit, IMP should be stored in a locked cupboard or room. However, there are no specific temperature requirements for vials of IMP prior to reconstitution. The Local Research Nurse (LRN) or another member of the study team, in collaboration with pharmacy, should ensure a suitable storage area is identified prior to the start of the study.
- AZTEC IMP kept in the hospital pharmacy should be stored in a designated area for IMPs. Records will be maintained in accordance with that pharmacy's standard operating procedures.

b) Prescribing, preparation and administration of trial medication

Prescribing

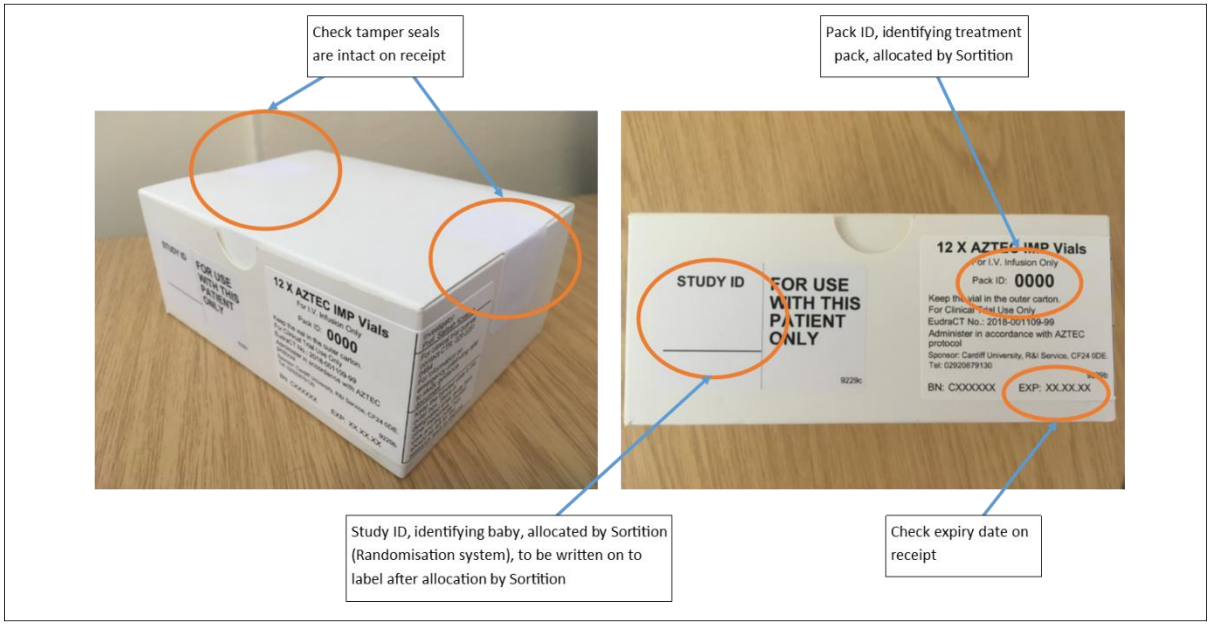
Once it has been confirmed that a baby meets the eligibility criteria, written informed consent has been obtained, and the baby has been randomised, the AZTEC trial medication can be prescribed.

- The allocated medication will be:
  - **AZTEC IMP**: 10 ml/kg once daily, for 3 days; followed by 5 ml/kg once daily, for 7 days (10 days total).
- Babies will be allocated a **four-digit** Treatment Pack ID number during randomisation. This number will correspond to a pack containing 12 vials of either azithromycin or placebo. You will not know whether the baby has been allocated azithromycin or placebo. In the event of an emergency, unblinding is possible (**see Protocol, Section 12.3 and guidance sheet 11: Withdrawal & Unblinding**).

- The randomisation system will also allocate a Study ID to each randomised baby. This will always begin with the letters "AZ", followed by a two-digit site identifier; the second two digits are a sequential participant identifier (e.g. "AZ1103" for the third baby recruited at site 11). The study ID should be recorded on the treatment pack, and on each vial. A space is provided on the label for this purpose.

- Azithromycin or placebo as an IMP must be prescribed electronically or on the baby's drug chart, to be given by intravenous injection. Due to the changing of dose after day 3, two separate prescriptions are recommended. Suggested wording is as follows:
  - '**AZTEC IMP. Doses 1-3, 10 ml/kg once daily; [enter 4-character numeric value e.g. Pack ID 1234]**'.
  - **AZTEC IMP. Doses 4-10, 5ml/kg once daily; [enter 4-character numeric value e.g. Pack ID 1234]**'.
  - **The chosen diluent should also be described**
- The Pack ID 'e.g. 1234' of the allocated pack is an essential component of the prescription.

- Prescribers must be trained in the related trial procedures, and this documented on the training and delegation logs.



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Preparation & administration

- Packs of trial medication **must only be** administered to the baby to whom it was allocated. If there is any doubt about which pack a vial has come from, discard the vial (recording it on the "**Daily Log" CRF**).

- Each vial is enclosed in a cardboard blinding carton. The blinding carton **must** stay intact at all times and must not be removed.

- The IMP is provided as powder. Therefore, a reconstitution step must first be performed. **A separate guidance sheet is provided with more detailed information (see Guidance sheet 5b: IMP administration).**

- The dose MUST then be further diluted before administration. A standard strength dilution is used, with the volume given adjusted by weight and day of dosing for the individual baby. See **Guidance sheet 5b** for details.

- The required volume of IMP should be administered intravenously as an infusion over **at least 60 minutes**. The first dose must be administered soon after randomisation and within 72 hours of birth at the latest.

- Once given, record the administration on the baby's drug chart as usual **and** on the **"Daily log" form**.

Dose administration					
IMP given today?	Weight used to calculate dose (g)	Dose given (mL)	Reason if not given	Number of vials used	Number of vials wasted
☒ Yes ☐ No	500	5	☐ No I.V. access ☐ Other[2]	1	0

- Each of the steps should also be initialled by the individual leading the preparation

Preparation steps (sign each)			
Add 4.8 mL water	Invert 5 times	Stand for 5 mins	1ml in 49 mL diluent
AB	AB	AB	AB

- Omitted doses and any wasted vials (due to dropping, damage, spillage, expiration or contamination) must also be recorded on **"Daily log" form. A reason should be provided for omitted doses**

- Safety information for Azithromycin is contained within the SmPC (section 4.6), which is in the Investigator Site File and Pharmacy File.

Practical considerations

- A list of compatible products which can be administered alongside the AZTEC IMP is included on **Guidance Sheet 5b: IMP administration**. A complete list can be found in the document box and Investigator Site File.

- Dosing errors must be recorded on **Dosing Error Form**. Dosing Error Forms should be faxed/emailed to the CTR immediately with any accompanying information (Fax: 020 3043 2376; Email: CTR-Safety@Cardiff.ac.uk). The form can be found in the Investigator Site file.

- In the event the **dosing is postponed** for practical or clinical reasons administer the daily dose as soon as it is deemed safe to do so. If a dose is postponed, please consider rescheduling further doses and **maintain a minimum period of at least 12 hours between doses. Treatment should not be extended beyond 10 days** (missed doses should not be added to the end).

c) Reconciliation of trial medication at end of treatment

- The trial team need to be able to account for each vial of the AZTEC trial medication. There are three documents involved in tracking allocated medication use: **the baby's standard drug chart**, **Daily log**, and the **Treatment Pack Reconciliation Form**.
- At the **end of the baby's IMP course** (10 days after commencing treatment (regardless of number of doses received, but usually after 10), permanent discontinuation of treatment, or death) please do the following:

- Cancel the prescription and retain all unused vials in the allocated pack
- Ensure all doses are recorded and complete the accountability totals on the "**Daily log" form**

Dose administration					
IMP given today?	Weight used to calculate dose (g)	Dose given (mg)	Reason if not given	Number of vials administered	Number of vials wasted
Accountability check at end of dosing				10	1

- Place any unused packs away from unused supplies of IMP, in a designated location
- **All used packs will undergo a final reconciliation process prior to disposal (see Guidance sheet 9: IMP supply and accountability)**.

- The study team are also asked, with input from the nurses who prepared and administered the IMP, to answer the following question and record the outcome on the **Daily Log**

In the current opinion of the study team has the baby received	☐ Azithromycin, ☐ Placebo, ☐ unable to tell

d) Discontinuation of treatment

The daily administration of the trial medication should continue until 10 days after the first dose. Omitted or missed doses should not be replaced with additional doses beyond these 10 days. The medication may be discontinued sooner than this if the baby is transferred to a non-recruiting site, if the baby dies, or at clinician or parental request.

Data collection should continue until discharge, or death, except if the baby is completely withdrawn from the trial at parental request. This sheet details what should happen in each circumstance.

Baby transfer

- Provision has been made for IMP to be transferred with the baby if they are being moved to an AZTEC recruiting centre, or a continuation site. The Trial Manager will notify each recruiting site of arrangements in their local networks during site initiation.

- If the IMP is being transferred, the treatment pack will be re-sealed using an **IMP Transfer Sticker**, located in your site's document box.

- More detail on transfers is given in **Guidance sheet 12a: Preparing a Transfer.** Final reconciliation of the IMP will then be performed at the receiving site.
- A "**Transfer" form** should be recorded to record data regarding the period of hospital stay.

Baby death

- If a baby dies before being discharged home, complete form **"Outcomes at 36 weeks PMA"** covering the period that the baby was an inpatient in your hospital
- In addition, please send a copy of the **discharge summary** and, if and when available, a copy of the **post-mortem examination report**.

Clinician decision to stop the medication permanently

- There will be very few instances where the clinician will need to permanently discontinue the medication. It will be far more common for the medication to be temporarily discontinued for clinical reasons, and restarted when it is deemed safe to do so
- If permanently discontinued, cancel the prescription, but the baby should **remain in the trial** and complete data collection procedures as normal.

Parent request to withdraw from the trial

- A parent has the right to withdraw their baby from the trial at any time and for any reason, without prejudice to the baby's care; they do not have to provide a reason for their decision.
- It is **important that you clarify** with the parent(s) whether, despite stopping the medication, they would agree to:
    - retention and use of the data already collected,
    - for samples to be collected, and
    - for data collection to continue to completion, i.e. an Oxygen Reduction Test (due at 36 weeks of postmenstrual age) (if applicable)
- After consulting the parents complete a **withdrawal form** recording their wishes regarding the withdrawal
- Cancel the baby's prescription, and, i**n all instances** retain the unused vials in the allocated pack. The research nurse will collect all used packs and initiate the reconciliation process.

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Summary flowchart