

CADISS Trial

(Cervical Artery Dissection in Stroke Study)
EudraCT: 2006-002827-18

Pharmacy Pack

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NB. This document is to be used only by staff trained in the CADISS study. This information pertains *only* to the IMP aspects of the CADISS study and is not a comprehensive guide. The purpose of this document is to clarify the process of medicines prescribing, supply, accountability and storage for investigators, nurses, and pharmacy staff.

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1. Introduction

CADISS is an open label trial to determine the feasibility of comparing anti-platelet therapy with anti-coagulation in the acute treatment of patients with cervical artery dissection. In this study heparin, dalteparin, warfarin, aspirin, clopidogrel and dipyridamole are all considered IMPs. The use of a stat dose of aspirin 300mg and clopidogrel 300mg is considered a NIMP and hence may be administered from usual ward supplies.

2. Prescribing for CADISS

2.1 Unfractionated Heparin

1. Prescribe unfractionated heparin by completing and signing the “Heparin Prescription Form” (Appendix 3)
2. Attach the completed “Heparin Prescription Form” securely to the inpatient drug chart
3. Also prescribe heparin in the usual place on the inpatient drug chart by writing:
“Heparin for CADISS Trial – See prescription attached”
4. Attach a “CADISS Alert Sticker” to the front of the inpatient chart (sample below)

<p><u>ALERT</u></p> <p>THIS PATIENT IS IN THE CADISS TRIAL</p> <p>THEY HAVE BEEN RANDOMISED TO ANTIPLATELETS/ANTICOAGULANTS*</p> <p>BETWEEN: DD/MM/YYYY & DD/MM/YYYY</p> <p>MEDICATIONS MUST BE FROM <u>PHARMACY TRIAL STOCK ONLY</u></p> <p>TO BE DISPENSED FROM PHARMACY ONLY</p> <p><small>*Please delete as required</small></p>

5. Also complete the “Anti-Coagulation Prescription Form” (Appendix 2) and send this down to pharmacy to order warfarin supplies
6. There are allocated stocks of “Heparin for CADISS” on the ward so the infusion can be started straight away
7. Inform the senior ward staff and ensure they understand how to administer medications for the CADISS Trial
8. Note: A heparin infusion protocol is printed on the prescription in Appendix 3. Trusts may use local heparin protocols, however, they must inform the sponsor and arrange for a new prescription form first. Sponsors need to approve use of a different regimen.

2.2 Dalteparin

1. Prescribe dalteparin by completing and signing the “Dalteparin Prescription Form” (Appendix 4)
2. Attach the completed “Dalteparin Prescription Form” securely to the inpatient drug chart
3. Also prescribe dalteparin in the usual place on the inpatient drug chart by writing:
“Dalteparin for CADISS Trial – See prescription attached”
4. Attach a “CADISS Alert Sticker” to the front of the inpatient chart (as above)
5. Also complete the “Anti-Coagulation Prescription Form” (Appendix 2) and send this down to pharmacy to order warfarin supplies
6. There are allocated stocks of “Dalteparin for CADISS” on the ward so injections may be administered straight away if necessary.
7. Inform the senior ward staff and ensure they understand how to administer medications for the CADISS Trial

2.3 Warfarin

1. Once supplies of “Warfarin for CADISS” are available on the ward (see point 5 above) the warfarin should be prescribed by completing the “Warfarin Prescription Form” (Appendix 5) and attaching this to the patient’s inpatient drug chart
2. Also prescribe warfarin in the usual place on the inpatient drug chart by writing:
“Warfarin for CADISS study – See prescription attached”
3. Attach a “CADISS Alert Sticker” to the front of the inpatient chart (as above)
4. Inform the senior ward staff, ensure that the “Warfarin for CADISS” has arrived from pharmacy, and that they understand how to administer medications for the CADISS Trial

2.4 Aspirin

1. Order aspirin supplies by completing and signing an “Anti-Platelet Prescription Form” (appendix 1) and sending it down to pharmacy.
2. Prescribe the aspirin by writing *“Aspirin for CADISS Study”, 75mg PO OD, DO NOT USE WARD STOCK* in the usual place in the inpatient drug chart
3. Attach a “CADISS Alert Sticker” to the front of the inpatient chart (as above)
4. Inform the senior ward staff, ensure that the “Aspirin for CADISS” has arrived from pharmacy, and that they understand how to administer medications for the CADISS Trial

2.5 Clopidogrel

1. Order clopidogrel supplies by completing and signing an “Anti-Platelet Prescription Form” (appendix 1) and sending it down to pharmacy.
2. Prescribe the clopidogrel by writing “*Clopidogrel for CADISS Study*”, *75mg PO OD, DO NOT USE WARD STOCK*” in the usual place in the inpatient drug chart
3. Attach a “CADISS Alert Sticker” to the front of the inpatient chart (as above)
4. Inform the senior ward staff, ensure that the “Clopidogrel for CADISS” has arrived from pharmacy, and that they understand how to administer medications for the CADISS Trial

2.6 Dipyridamole

1. Order dipyridamole supplies by completing and signing an “Anti-Platelet Prescription Form” (appendix 1) and sending it down to pharmacy.
2. Prescribe the dipyridamole by writing “*Dipyridamole for CADISS Study*”, *200mg MR PO BD, DO NOT USE WARD STOCK*” in the usual place in the inpatient drug chart
3. Attach a “CADISS Alert Sticker” to the front of the inpatient chart (as above)
4. Inform the senior ward staff, ensure that the “Dipyridamole for CADISS” has arrived from pharmacy, and that they understand how to administer medications for the CADISS Trial

3. Managing CADISS Medicines on the Ward

3.1 Supply

- Stocks of “Heparin for CADISS” and “Dalteparin for CADISS” will be provided by the Pharmacy Department and be kept in an approved area on the ward. Only one strength of dalteparin will be supplied (10,000 unit/ml ampoule) and this can be used to administer any prescribed dose to CADISS patients. Heparin will be supplied as 25,000 unit/5ml ampoules.
- Supplies will be ordered by the local investigator who will inform the senior ward staff when stocks are available on the ward.
- Quantities of drug used will be recorded (“Booked out”) on forms “Ward Heparin Accountability” and “Ward Dalteparin Accountability” (appendices 6 and 7, respectively).

3.2 Storage

3.2.1 Heparin and Dalteparin for CADISS

- Stocks of “Heparin for CADISS” and “Dalteparin for CADISS” will need to be stored on the ward for immediate administration to randomised patients.
- The storage place must be in a temperature controlled area (15-25C) and restrict the access of unauthorised personnel.
- The allocated place must be agreed between the investigator and senior ward staff and approved by the local Pharmacy Department

3.2.2. Warfarin, Dipyridamole, Aspirin + Clopidogrel for CADISS

- Supplies of warfarin, dipyridamole, clopidogrel and aspirin will be dispensed by the Pharmacy Department against a prescription (see section 2, above).
- Once dispensed these may be stored in Patients’ Own Drug (POD) lockers or on ward trolleys/cupboard as per local procedure
- Dispensed items do not require further temperature monitoring as they are considered to be in the patients possession at the point of dispensing (where usually all temperature control would cease)

3.3 Ward Temperature Monitoring

The temperature of the medicines storage area must be measured daily (including sat/sun/bank holidays) and recorded on the “Temperature Monitoring Form” (appendix 8). This responsibility is delegated to the local investigator (ultimate responsibility lies with the Pharmacy Department) who may in turn delegate this responsibility to ward staff. If a temperature reading is outside the required specifications (< 15°C or > 25°C) then, move the stock to a temperature controlled environment and inform the Sponsor immediately.

3.4 Issuing/Administering Medicines to Patients

3.4.1 Heparin and Dalteparin

- When issuing “Heparin for CADISS” or “Dalteparin for CADISS” to individual patients the respective accountability forms must be completed (appendix 6 and 7, as previous).
- Additionally the prescription form attached to the inpatient drug chart must also be fully completed

3.4.2 Warfarin

- Warfarin is issued from the Pharmacy and will be labelled with the patients name and a “CADISS Sponsor Label”
- Do NOT administer ward stock against a CADISS prescription
- Administration is recorded by completing the “Warfarin Prescription Chart” (appendix 5) attached to the patient’s inpatient chart

3.4.3 Dipyridamole, Aspirin & Clopidogrel

- Dipyridamole, aspirin and clopidogrel are issued from the Pharmacy and will be labelled with the patient’s name and a “CADISS Sponsor Label”
- Do NOT administer ward stock against a CADISS prescription
- Administration is recorded on the inpatient chart in the usual way.

4. Discharging Patients

- Ensure that patients have a sufficient supply of trial medicines at discharge
- The investigator must make a copy of the patient’s inpatient chart and any additional CADISS prescription forms (e.g. heparin, warfarin, dalteparin) for their records
- The originals are to be stored with the patient notes

5. Pharmacy Considerations:

5.1 Getting Started

- Ensure there is a current signed Memorandum of Understanding or Sponsorship agreement between your site and the Sponsor
- Agree a storage area on the ward and inform sponsor
- Issue the investigator with a thermometer, stocks of dalteparin and heparin, and accountability forms for ward storage
- Issue “CADISS Patient Alert” stickers (for the inpatient chart) to research team.
- Ensure you have a supply of “CADISS Sponsor Label” to be attached to all trial stock
- Note: Switching between anti-platelets during the trials (e.g. in the case of intolerability) is permitted. Record this in the Pharmacy Randomisation Log (Appendix 10)

- Note: if your institution needs to use a LMWH other than dalteparin then, this is permissible, but the sponsor must be informed as different prescription and monitoring forms need to be agreed before the study can start.

5.2 Source of IMP

The brand of all IMPs:

- Aspirin 75mg tablets
- Clopidogrel 75mg tablets
- Dipyridamole MR 200mg capsules
- Warfarin 1mg and 3mg tablets
- Dalteparin 10,000 unit/ml ampoule
- Heparin 25,000 unit/5ml amp/vial

May be chosen by each local Trust according to local contracts. The chosen brand must be recorded with each dispensing. If local contracts change, or supply issues arise during the study then the brands may be changed as long as this is recorded.

5.2 Storage

- IMPs must be stored in a temperature controlled environment (15-25°C) with restricted access to unauthorised personnel
- The temperature in the allocated storage area must be monitored and recorded daily using the “Pharmacy Temperature Monitoring Form” (Appendix 9)
- Local Trusts may use local forms for recording daily temperatures but this must be agreed with the Sponsor first
- Where stocks of IMP are issued for storage on the wards (heparin and dalteparin) the local Pharmacy Department remains ultimately responsible for the storage and temperature monitoring of these medicines.
- This responsibility may be delegated to the local investigator or ward staff according to local, documented arrangements.

5.3 Labelling

- As all CADISS IMPs are licensed medicines being used within their marketing authorisations then reduced labelling requirements apply (as per “MHRA Rules and Guidance for Pharmaceutical Manufacturers and Distributors”, 2007, MHRA)
- A “CADISS Sponsor Label” must be attached to ALL IMPs either issued to the wards as stock or dispensed to patients
- Patient instructions for aspirin, dipyridamole and clopidogrel are specified on the “Anti-Platelet Prescription Form” (appendix 1.)
- Patient instructions for warfarin 1mg and 3mg tablets are specified on the “Anti-Coagulation Prescription Form” (appendix 2.)

5.4 Accountability and Documentation

- Randomisation is conducted by the investigator, however, Pharmacy should keep a record of patient names and whether they are in the anti-platelet or anti-coagulation arms, using the “Pharmacy Randomisation Log” (Appendix 10).
- There is also a separate accountability form for each IMP (appendices 11-16) which must be completed on each occasion that IMP are dispensed for a patient or issued to the ward
- These accountability forms may also be used to record IMP returns
- At the close of the study any “Ward Accountability Forms” (appendices 6 and 7) must be returned to Pharmacy along with any IMP stocks for reconciliation at study closure.
- Destroy any returned or unwanted medication as per local waste policy
- Completed prescriptions are to be filed in a dedicated study folder after each dispensing
- Storage and retention of all documentation should be conducted as per ICH-GCP standards



APPENDICES

CADISS Trial

**(Cervical Artery Dissection in Stroke Study)
EudraCT: 2006-002827-18**

Anti-Platelet Prescription Form

CADISS (Cervical Artery Dissection in Stroke Study)
EudraCT: 2006-002827-18

Chief Investigators Names: Prof. J. Norris/Prof. H. Markus				Local Investigator:	
Patient Name:				Patient Date of Birth:	DD/MM/YYYY
Patient Trial Number:	NNN	- 1 1 -	YY	Patient Hospital Number:	

Please indicate anti-platelet regimen by ticking boxes and signing below:

<p>Aspirin 75mg Tablet:</p> <p>Dose: 300mg po stat then 75mg po OD thereafter for 3 months</p> <p>Label: "Take ONE tablet ONCE daily, with or after food" (also add additional sponsor label to each pack)</p> <p><i>Quantity to be dispensed: 3 packs x 28 or 30 tabs</i></p> <table border="1"> <thead> <tr> <th>Amount:</th> <th>Dispensed by:</th> <th>Checked By:</th> <th>Date:</th> </tr> </thead> <tbody> <tr> <td>3 x 28 or 3 x 30 (circle one)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>				Amount:	Dispensed by:	Checked By:	Date:	3 x 28 or 3 x 30 (circle one)				<input type="checkbox"/>
Amount:	Dispensed by:	Checked By:	Date:									
3 x 28 or 3 x 30 (circle one)												
OR												
<p>Clopidogrel 75mg Tablets</p> <p>Dose: 300mg po stat then 75mg po od thereafter for 3 months</p> <p>Label: "Take ONE tablet ONCE daily" (also add additional sponsor label to each pack)</p> <p><i>Quantity to be dispensed: 3 packs x 28 tabs</i></p> <table border="1"> <thead> <tr> <th>Amount:</th> <th>Dispensed By:</th> <th>Checked By:</th> <th>Date:</th> </tr> </thead> <tbody> <tr> <td>3 x 28 or 3 x 30 (circle one)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>				Amount:	Dispensed By:	Checked By:	Date:	3 x 28 or 3 x 30 (circle one)				<input type="checkbox"/>
Amount:	Dispensed By:	Checked By:	Date:									
3 x 28 or 3 x 30 (circle one)												

If prescribed ASPIRIN patients may also be prescribed:

<p>Dipyridamole 200mg SR Capsules</p> <p>Dose: 200mg po bd</p> <p>Label: "Take ONE capsule TWICE daily. Swallow Whole with or after food." (add additional sponsor label to each pack)</p> <p><i>Quantity to be dispensed: 3 packs x 60 caps</i></p> <table border="1"> <thead> <tr> <th>Amoun:</th> <th>Dispensed By:</th> <th>Checked By:</th> <th>Date:</th> </tr> </thead> <tbody> <tr> <td>3 x 60</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>				Amoun:	Dispensed By:	Checked By:	Date:	3 x 60				<input type="checkbox"/>
Amoun:	Dispensed By:	Checked By:	Date:									
3 x 60												

Signature of Investigator:		Date:	DD/MM/YYYY
Print Name of Investigator:		Bleep/Ext:	

Anticoagulation Prescription Form

CADISS (Cervical Artery Dissection in Stroke Study)

EudraCT: 2006-002827-18

Chief Investigators Names: Prof. J. Norris/Prof. H. Markus			Local Investigator:	
Patient Name:			Patient Date of Birth:	DD/MM/YYYY
Patient Trial Number:	NNN	- 1 1 -	YY	Patient Hospital No.:

Please indicate anticoagulation regimen by ticking boxes and signing below:

Dalteparin

(also complete Appendix 4 "Dalteparin Prescription Form")
Use CADISS stock from ward – do not dispense

OR

Unfractionated Heparin

(also complete Appendix 3 "Heparin Prescription Form")
Use CADISS stock from ward – do not dispense

AND

Warfarin

Dose: As per INR (to maintain INR 2-3)

Pharmacy: (dispense both strengths, label "Take according to your anti-coagulation prescription", and add sponsor label to each pack)

Warfarin Strength	Amount Dispensed:	Dispensed By:	Checked By:	Date:
1mg tablet	3 x 28 or 3 x 30 (circle one)			
3mg tablet	2 x 28 or 2 x 30 (circle one)			

Signature of Investigator:		Date:	DD/MM/YYYY
Print Name of Investigator:		Bleep/Ext:	

Affix Patient Addressograph Here
Patient Name, Hospital Number, Date of Birth

Intravenous Heparin Infusion Prescription Form
CADISS (Cervical Artery Dissection in Stroke Study)
EudraCT: 2006-002827-18

Chief Investigator: Prof. J. Norris/Prof. H. Markus
Local Investigator:.....

Patient Trial Number:

The target therapeutic range for APTTR (using synthetic reagent) is 1.5-3.5. Check APTTR 6 hours after infusion starts (and after any dose change) and adjust as follows:

APTTR:	Action:
>6	Stop for one hour, reduce by 500 units/hour (1 ml/h)
5.3-5.9	Reduce by 300 units/h (0.6 ml/h)
4.7-5.2	Reduce by 200 units/h (0.4 ml/h)
4.1-4.6	Reduce by 100 units/h (0.2 ml/h)
3.6-4.1	Reduce by 50 units/h (0.1 ml/h)
1.5-3.5	NO CHANGE
1.2-1.4	Increase by 200 units/h (0.4 ml/h)
< 1.2	Increase by 400 units/h (0.8 ml/h)

**NB: Use only specially marked "Heparin for CADISS Trial" stock for this patient.
Do NOT use ward stock! If unsure ask the Prescribing Doctor!**

Administration: Draw up 25,000 units of "Unfractionated Heparin for CADISS Trial" into a 50ml syringe and dilute to 50ml with sodium chloride 0.9% resulting in a concentration of 500 units/ml. Start intravenous infusion at 2 ml/h and adjust according to APTTR as above.

APTTR Sample taken	APTTR Value	Heparin Infusion Rate:	Prescribers Signature and date	Batch Number (Heparin)	Infusion Started (date)	Infusion Started (time)	Nurse signature	Nurse Witness signature	Infusion Stopped (date)	Infusion Stopped (time)
NA	NA	2 ml/h								

Prescription of

Attach additional prescription form to drug chart if necessary

Affix Patient Addressograph Here
Patient Name, Hospital Number, Date of Birth

Dalteparin Prescription Form
CADISS (Cervical Artery Dissection in Stroke Study)
EudraCT: 2006-002827-18

Chief Investigator: Prof. J. Norris/Prof. H. Markus
Local Investigator:.....

Patient Trial Number:

Dose	Weight:	Dose:	Volume per dose
	<46kg	7,500 units OD	0.75ml
	46-56kg	10,000 units OD	1.0ml
	57-68kg	12,500 units OD	1.25ml
	69-82kg	15,000 units OD	1.5ml
	>83kg	18,000 units OD	1.8ml

NB: Use only specially marked "Dalteparin for CADISS Trial 10,000 units/ml Ampoules" for this patient. Do NOT use ward stock! If unsure check with the prescriber before administering

Administration: Draw up required volume of dalteparin 10,000 unit/ml into a syringe and administer by subcutaneous injection ONCE daily recording below.

Required Dalteparin Dose per Day: (units)						
Time (circle one):	0800	1200	1400	1800	2200	2400
Prescriber Signature:						
Prescriber Name (print):						
Date Given	Time given	Given by:			Dalteparin Batch Number	

Prescription of

Attach additional prescription form to drug chart if necessary

Pharmacy Randomisation Log
CADISS Trial
EudraCT No: 2006-002827-18

Chief Investigator: Professor John Norris/ Professor Hugh Markus **Site :**
CADISS Research team contact: Jennifer Peycke tel: 020 8266 6468

Principal Investigator:
Local Research Team Contact:

Date	Patient Name	Hospital Number	Trial Number	Therapy randomised to indicate		Entered by
				Anti-platelet	Anti-coagulation	
				Aspirin Aspirin + dipyridamole Dipyridamole Clopidogrel <i>(circle one)</i>	Dalteparin + warfarin Heparin + warfarin <i>(circle one)</i>	
				Aspirin Aspirin + dipyridamole Dipyridamole Clopidogrel <i>(circle one)</i>	Dalteparin + warfarin Heparin + warfarin <i>(circle one)</i>	
				Aspirin Aspirin + dipyridamole Dipyridamole Clopidogrel <i>(circle one)</i>	Dalteparin + warfarin Heparin + warfarin <i>(circle one)</i>	
				Aspirin Aspirin + dipyridamole Dipyridamole Clopidogrel <i>(circle one)</i>	Dalteparin + warfarin Heparin + warfarin <i>(circle one)</i>	
				Aspirin Aspirin + dipyridamole Dipyridamole Clopidogrel <i>(circle one)</i>	Dalteparin + warfarin Heparin + warfarin <i>(circle one)</i>	

DALTEPARIN
10,000 units/ml Ampoules

Pharmacy Accountability Form
CADISS TRIAL

EudraCT No: 2006-002827-18

Chief Investigator: Professor John Norris/ Professor Hugh Markus
CADISS research team contact: Jennifer Peycke tel: 020 8266 6468

Site no:

Principal Investigator:
Local research team contact:

Date	Ward/ Dept	Qty issued	Manufacturer	Batch number	Expiry Date	Returns – qty, date recorded	Signature

HEPARIN
25,000 units/5ml Ampoule or Vial

Pharmacy Accountability Form
CADISS TRIAL

EudraCT No: 2006-002827-18

Chief Investigator: Professor John Norris/ Professor Hugh Markus
CADISS research team contact: Jennifer Peycke tel: 020 8266 6468

Site no:

Principal Investigator:
Local research team contact:

Date	Ward/ Dept	Qty issued	Manufacturer	Batch number	Expiry Date	Returns – qty, date recorded	Signature

