Orodispersible Minitablets of Enalapril in young children with Heart Failure due to Congenital Heart Disease (WP09 Trial)

Published: 12-10-2015
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Primary:To obtain paediatric pharmacokinetic data of enalapril and its active metabolite enalaprilat in patients treated with enalapril ODMTs to describe the dose exposure in the paediatric population with CHD. Secondary:1. To demonstrate safety of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital cardiac disorders
Study type	Interventional

Summary

ID

NL-OMON45974

Source
ToetsingOnline

Brief title
WP09 Trial

Condition

- Congenital cardiac disorders

Synonym
Congenital heart disease, heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Ethicare GmbH
Source(s) of monetary or material Support: LENA consortium door financiering van de Europese Unie.

Intervention

Keyword: Congenital Heart Disease, Enalapril, Paediatrics, Pharmacokinetics

Outcome measures

Primary outcome

The bioavailability of enalapril and its active metabolite enalaprilat in young children (AUC from 0 to time of last sampling point, Cmax and Tmax); descriptive pharmacokinetic investigation.

Secondary outcome

1. The bioavailability of enalapril and its active metabolite enalaprilat in the different age subsets (0 to *12 months and 12 months to *6 years) of the paediatric study population (AUC from 0 to time of last sampling point, Cmax and Tmax); descriptive pharmacokinetic investigation.

2. Markers of the renin-angiotensin-aldosterone system as exploratory pharmaco-dynamic investigation.

3. Brain natriuretic peptides (BNPs).

4. Acceptability and palatability of the novel formulation.

5. Safety parameters including blood pressure and renal function.

6. Echocardiography (Shortening Fraction).

7. Rehospitalisation due to heart failure including the need for heart transplantation or the institution of mechanical circulatory support.

8. Death due to worsening of the underlying disease.

9. Pharmacodynamic and efficacy endpoints analysis to differentiate high and low output disease.

Study description

Background summary

Enalapril maleate has established medical use having been marketed in Europe since 1983. Its safety and efficacy in adults are therefore well understood, although less so in paediatric patients since few clinical studies have been conducted in this population. The European Medicines Agency Expert Group Meeting on Paediatric Heart Failure considers enalapril a first-line treatment for chronic heart failure in children (EMA, 2010a).
There is currently no licensed formulation of enalapril available in Europe suitable for use in children with heart failure, resulting in the administration of extemporaneous oral preparations.
This study will enable the development of a novel clinically relevant age-appropriate and acceptable enalapril formulation, with improved method of administration and ease of dosing compared to products currently available.

Study objective

Primary:
To obtain paediatric pharmacokinetic data of enalapril and its active metabolite enalaprilat in patients treated with enalapril ODMTs to describe the dose exposure in the paediatric population with CHD.

Secondary:
1. To demonstrate safety of enalapril ODMTs in children with CHD.
2. To characterise the dose/safety relationship from a starting dose to an optimal maintenance dose.
3. To explore the dose exposure/response relationship with pharmacodynamic parameters in the paediatric population with CHD.
4. To investigate the Shortening Fraction (SF) of the heart muscle by echocardiography.
5. To investigate the acceptability and palatability of enalapril ODMTs in the paediatric population with CHD.

Study design

Phase II/III prospective, open-label, single and multiple dose pharmacokinetic bridging study with exploratory pharmacodynamic assessments in patients from birth to less than 6 years of age.

Intervention

GROUP A
First dose: clinically comparable dosing of ACEI previously used

GROUP B
First dose of one or two 0.25 mg ODMTs in accordance with the dose banding dosing regimen provided in this protocol, administered orally. If there is no sustained hypotension as determined by common clinical practice during the 8 hours blood pressure surveillance period under the initial dose, daily administration of the first dose will be continued for one week or shorter if the clinical condition of the child requires more rapid up-titration. Daily doses will be increased until the individually defined long-term dose is reached as long as there is no sustained hypotension and serum creatinine and potassium are acceptable as determined by common clinical practice before each dose increase, respecting the agreed stopping rules.
First and second titration doses in children below 7 kg will be administered in dispersed form if deemed appropriate by the investigator.

Study burden and risks

nvt

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- Age from birth to 6 years.
- Male and female patients.
- Weight greater than 2.5 Kg.
- Diagnosis of heart failure due to congenital heart disease requiring after load reduction by drug therapy.
- Subjects may be naïve to ACEI.
- Subjects already on ACEI willing to switch to Enalapril Orodispersable Minitablets.
- Patient and/or parent(s)/legal representative provided written informed consent and assent from the patient received according to national legislation and as far as achievable from the child.
- Permitted: other CHF medications are allowed, at the discretion of the investigator. These include but are not limited to diuretics, beta-blockers, digoxin, mineralocorticoid receptor antagonist, aspirin and paracetamol.

Exclusion criteria

- Neonates if born < 37 weeks gestation.
- Severe HF and/or end stage heart failure requiring ICU support precluding introduction or continuation of ACEI.
- Too low blood pressure, e.g. - Uncorrected primary obstructive valvular disease, or significant systemic ventricular outflow obstruction, dilated restrictive or hypertrophic cardiomyopathy.
- Uncorrected severe peripheral stenosis of large arteries including severe coarctation of the aorta.
- Severe renal impairment with Serum creatinine >2x ULN.
- History of Angioedema.
- Hypersensitivity to ACEI.
- Concomittant medication:
o Dual ACEI therapy
o Renin inhibitors
o Angiotensin II antagonists
o NSAIDs (including ibuprofen) except acetylsalicylic acid only for antiplatelet therapy.
- Already enrolled in an interventional trial with an investigational drug, unless no interference with the current study can be shown.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-12-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Enalapril orodispersible minitablet 0,25mg
Generic name:	Enalapril Maleate orodispersible minitablet 0,25mg
Product type:	Medicine
Brand name:	Enalapril orodispersible minitablet 1,0mg
Generic name:	Enalapril Maleate orodispersible minitablet 1,0mg

Ethics review

Approved WMO Date:	12-10-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-12-2015
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-002396-18-NL
CCMO	NL54738.078.15