



Clinical trial results:

A multicentre, randomised, double-blind, two arm, parallel group, placebo controlled, pilot study to assess the effect of Gaviscon Advance as add-on therapy in GORD patients with inadequate response to once daily proton pump inhibitor treatment.

Summary

EudraCT number	2011-005486-21
Trial protocol	DK DE
Global end of trial date	14 November 2013

Results information

Result version number	v1 (current)
This version publication date	11 June 2017
First version publication date	11 June 2017

Trial information

Trial identification

Sponsor protocol code	GA1102
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Reckitt Benckiser Healthcare (UK) Ltd
Sponsor organisation address	Dansom Lane, Hull, United Kingdom, HU8 7DS
Public contact	Medical Director, Gastroenterology, Clearcut Clinical Consulting Ltd., +44 7813731925,
Scientific contact	Medical Director, Gastroenterology, Clearcut Clinical Consulting Ltd., +44 7813731925,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2013
Global end of trial reached?	Yes
Global end of trial date	14 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the efficacy of Gaviscon Advance (an aniseed flavoured oral suspension) compared with placebo in the suppression of GORD symptoms in patients whose symptoms are inadequately controlled by once daily PPI therapy alone.

Protection of trial subjects:

This study was conducted in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki, as referenced in EU Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 74
Country: Number of subjects enrolled	Germany: 62
Worldwide total number of subjects	136
EEA total number of subjects	136

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	94
From 65 to 84 years	41
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was multicentre and multinational with 8 active centres in Denmark and Germany.

Pre-assignment

Screening details:

A total of 195 patients were screened for the study, of which 59 patients were screen failures and 136 patients were randomized.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Gaviscon Advance

Arm description:

Gaviscon Advance 10 ml taken 4 times a day for 7 days.

Arm type	Experimental
Investigational medicinal product name	Gaviscon Advance
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

10 ml taken 4 times a day for 7 days.

Arm title	Placebo
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Arm description:

Placebo 10 ml taken 4 times a day for 7 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

10 ml taken 4 times a day for 7 days.

Number of subjects in period 1	Gaviscon Advance	Placebo
Started	66	70
Completed	65	68
Not completed	1	2
Adverse Event	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Gaviscon Advance
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Reporting group description:

Gaviscon Advance 10 ml taken 4 times a day for 7 days.

Reporting group title	Placebo
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Reporting group description:

Placebo 10 ml taken 4 times a day for 7 days.

Reporting group values	Gaviscon Advance	Placebo	Total
Number of subjects	66	70	136
Age categorical			
Safety Population: All patients who were recruited to the study and received at least one dose of IMP. This population was used for summaries of safety and also for baseline data.			
Units: Subjects			
Adults (18-64 years)	44	50	94
From 65-84 years	21	20	41
85 years and over	1	0	1
Age continuous			
Safety population			
Units: years			
arithmetic mean	57.4	55.4	
standard deviation	± 13.97	± 14.79	-
Gender categorical			
Safety population			
Units: Subjects			
Female	42	46	88
Male	24	24	48
Ethnicity			
Safety population			
Units: Subjects			
Caucasian	66	68	134
Asian	0	2	2
Smoking habits			
Safety population			
Units: Subjects			
Never	37	29	66
Former	17	26	43
Current	12	15	27
Alcohol consumption			
Safety population			
Units: Subjects			
Never	37	36	73
Former	1	3	4
Current	28	31	59
Caffeine consumption			
Safety population			
Units: Subjects			

Never	5	12	17
Former	2	1	3
Current	59	57	116
Height			
Safety population			
Units: cm			
arithmetic mean	170	169.8	
standard deviation	± 11.07	± 9.45	-
Weight			
Safety population			
Units: kg			
arithmetic mean	81.6	81	
standard deviation	± 17.25	± 20.35	-
BMI			
Safety population			
Units: kg/m ²			
arithmetic mean	28.13	27.99	
standard deviation	± 4.855	± 6.454	-

End points

End points reporting groups

Reporting group title	Gaviscon Advance
Reporting group description: Gaviscon Advance 10 ml taken 4 times a day for 7 days.	
Reporting group title	Placebo
Reporting group description: Placebo 10 ml taken 4 times a day for 7 days.	

Primary: Change from Baseline to Post-Dose in HRDQ score (heartburn and regurgitation only)

End point title	Change from Baseline to Post-Dose in HRDQ score (heartburn and regurgitation only)
End point description: Intention to treat (ITT) population: All patients who were recruited to the study and had at least 1 day of complete HRDQ (Heartburn and Dyspepsia) data post-dosing. This population was used for summaries of efficacy and baseline data. Two patients with no post-baseline HRDQ data were excluded from ITT population. Heartburn Regurgitation and Dyspepsia Questionnaire (HRDQ): The HRDQ symptom severity was recorded a 0 (no symptoms), 1 (mild), 2 (moderate) and 3 (severe) and the frequency was scored as 0 (none), 1 (once), 2 (twice), 3 (thrice), 4 (4 or 5 times), 5 (6 – 10 times) and 6 (more than 10 times or constant). In addition, the HRDQ questionnaire required patients to record the duration of their symptoms and whether or not they had experienced night-time symptoms.	
End point type	Primary
End point timeframe: From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-4.95 (± 4.69)	-3.48 (± 5.51)		

Statistical analyses

Statistical analysis title	Change in HRDQ Score (heartburn and regurgitation)
Statistical analysis description: Intention to treat (ITT) population: All patients who were recruited to the study and had at least 1 day of complete HRDQ (Heartburn and Dyspepsia) data post-dosing. This population was used for summaries of efficacy and baseline data. Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	
Comparison groups	Gaviscon Advance v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0321
Method	ANCOVA

Secondary: Change in HRDQ Score – Dyspepsia

End point title	Change in HRDQ Score – Dyspepsia
End point description: ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
End point type	Secondary
End point timeframe: From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-1.68 (± 2.98)	-1.08 (± 3.21)		

Statistical analyses

Statistical analysis title	Change in HRDQ Score – Dyspepsia
Statistical analysis description: ITT population. Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4845
Method	ANCOVA

Secondary: Change in HRDQ Score – Heartburn

End point title	Change in HRDQ Score – Heartburn
End point description: ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
End point type	Secondary

End point timeframe:

From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-2.74 (± 2.56)	-1.9 (± 3.27)		

Statistical analyses

Statistical analysis title	Change in HRDQ Score – Heartburn
Statistical analysis description:	
Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0244
Method	ANCOVA

Secondary: Change in HRDQ Score – Regurgitation

End point title	Change in HRDQ Score – Regurgitation
End point description:	
ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
End point type	Secondary
End point timeframe:	
From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-2.2 (± 2.53)	-1.55 (± 2.71)		

Statistical analyses

Statistical analysis title	Change in HRDQ Score – Regurgitation
Statistical analysis description: Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1045
Method	ANCOVA

Secondary: Change From Baseline to Post-Dose in Number of Days with Night Time Symptoms

End point title	Change From Baseline to Post-Dose in Number of Days with Night Time Symptoms
End point description: ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
End point type	Secondary
End point timeframe: From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: Number of days				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-1.66 (± 2.56)	-0.6 (± 1.74)		

Statistical analyses

Statistical analysis title	Change in Number of Days with Night Time Symptoms
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0083
Method	ANCOVA

Secondary: Change From Baseline to Post-Dose in Duration of Symptoms (HRDQ)

End point title	Change From Baseline to Post-Dose in Duration of Symptoms (HRDQ)
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End point description:	
ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
End point type	Secondary
End point timeframe:	
From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	68		
Units: minute				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-73.58 (\pm 222.57)	-66.92 (\pm 201.44)		

Statistical analyses

Statistical analysis title	Change in Duration of Symptoms
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6494
Method	ANCOVA

Secondary: Change From Baseline to Post-Dose in Frequency of Heartburn (HRDQ Score)

End point title	Change From Baseline to Post-Dose in Frequency of Heartburn (HRDQ Score)
End point description:	
ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
End point type	Secondary
End point timeframe:	
From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: Number of events				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-1.21 (\pm 1.06)	-0.78 (\pm 1.14)		

Statistical analyses

Statistical analysis title	Change in Duration of Symptoms
Statistical analysis description: Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0114
Method	ANCOVA

Secondary: Change From Baseline to Post-Dose in Frequency of Regurgitation (HRDQ Score)

End point title	Change From Baseline to Post-Dose in Frequency of Regurgitation (HRDQ Score)
End point description: ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
End point type	Secondary
End point timeframe: From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: Number of events				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-1.03 (\pm 1.08)	-0.63 (\pm 1.19)		

Statistical analyses

Statistical analysis title	Change in Frequency of Regurgitation
Statistical analysis description: Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	
Comparison groups	Gaviscon Advance v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0364
Method	ANCOVA

Secondary: Change From Baseline to Post-Dose in Frequency of Dyspepsia (HRDQ Score)

End point title	Change From Baseline to Post-Dose in Frequency of Dyspepsia (HRDQ Score)
End point description: ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
End point type	Secondary
End point timeframe: From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: Number of events				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-0.83 (± 1.23)	-0.48 (± 1.22)		

Statistical analyses

Statistical analysis title	Change in Frequency of Dyspepsia
Statistical analysis description: Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	
Comparison groups	Placebo v Gaviscon Advance
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1857
Method	ANCOVA

Secondary: Change From Baseline to Post-Dose in ReQuest GI Scores

End point title	Change From Baseline to Post-Dose in ReQuest GI Scores
End point description: ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
ReQuest GI is a self-assessed, dimension-orientated scale designed to evaluate treatment response on a	

daily basis in patients suffering from GORD. The scale assesses 4 dimensions of GORD. Intensity is measured on a 100-mm VAS and frequency on a 7-point Likert scale (0 to 10 times/constant per day). The range of the ReQuest™ GI score is from 0 reflecting no symptoms to 30.77 reflecting the highest severity/frequency of symptoms.

End point type	Secondary
End point timeframe:	
From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	61		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-2.8 (± 3.3)	-2.37 (± 3.49)		

Statistical analyses

Statistical analysis title	Change in ReQuest GI scores
Statistical analysis description:	
Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3138
Method	ANCOVA

Secondary: Change From Baseline to Post-Dose in the Patient Satisfaction Score

End point title	Change From Baseline to Post-Dose in the Patient Satisfaction Score
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End point description:

ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.

Patient Satisfaction Visual Analogue Scale (VAS): Patient satisfaction with IMP in controlling their symptoms was assessed in response to the question: 'Thinking back over the past 7 days and the medication you received, how satisfied are you with the control of your symptoms?' Patients drew a perpendicular line on a 100-mm VAS, with anchors at 0 = 'Very Satisfied' and 100 = 'Very Dissatisfied' to reflect their satisfaction.

End point type	Secondary
End point timeframe:	
From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	67		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	-2.6 (\pm 3.18)	-2.1 (\pm 3.01)		

Statistical analyses

Statistical analysis title	Change in Patient Satisfaction Score
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1959
Method	ANCOVA

Secondary: Change From Baseline in Number of Symptom-Free Days (HRDQ)

End point title	Change From Baseline in Number of Symptom-Free Days (HRDQ)
End point description:	
ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.	
A symptom-free day is defined as a day where the respective symptoms: heartburn, regurgitation and dyspepsia (all derived from the HRDQ) had a value for frequency of 0.	
End point type	Secondary
End point timeframe:	
From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)	

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: day				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	0.71 (\pm 1.27)	0.61 (\pm 1.71)		

Statistical analyses

Statistical analysis title	Change Number of Symptom Free Days (HRDQ)
Statistical analysis description:	
Two patients with no post-baseline HRDQ data available is exclusion from Intention-to-treat population.	

Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9363
Method	ANCOVA

Secondary: Change From Baseline in Number of Symptom-Free Days (ReQuest)

End point title	Change From Baseline in Number of Symptom-Free Days (ReQuest)
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End point description:

ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.

ReQuest GI is a self-assessed, dimension-orientated scale designed to evaluate treatment response on a daily basis in patients suffering from GORD. The scale assesses 4 dimensions of GORD. Intensity is measured on a 100-mm VAS and frequency on a 7-point Likert scale (0 to 10 times/constant per day). The range of the ReQuest™ GI score is from 0 reflecting no symptoms to 30.77 reflecting the highest severity/frequency of symptoms.

A symptom-free day is defined as a day where the respective symptoms: acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints and nausea (all derived from ReQuest™) had a value for frequency of 0.

End point type	Secondary
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End point timeframe:

From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	68		
Units: day				
arithmetic mean (standard deviation)				
Change from baseline to post-dose	0.55 (± 1.68)	0.56 (± 1.49)		

Statistical analyses

Statistical analysis title	Change in Number of Symptom Free Days (ReQuest)
Comparison groups	Gaviscon Advance v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8195
Method	ANCOVA

Secondary: Change from baseline to post-dose in whether the patient had any night-time symptoms (HRDQ)

End point title	Change from baseline to post-dose in whether the patient had any night-time symptoms (HRDQ)
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End point description:

ITT population. Two patients with no post-baseline HRDQ data were excluded from ITT population.

-1 = Improvement in night time symptoms (i.e. patients had night-time symptoms at baseline and no night time symptoms post-dose)

0 = Either night-time symptoms at baseline and post-dose or no night-time symptoms at baseline and post-dose

1 = Deterioration in night-time symptoms (i.e. patients had no night-time symptoms at baseline and night time symptoms post-dose)

End point type	Secondary
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End point timeframe:

From Visit 2 (Day 0-Baseline) to Visit 3 (Day 8, 9 or 10)

End point values	Gaviscon Advance	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: Number of patients				
-1: Improvement in night-time symptoms	16	8		
0: No night-time symptoms at baseline & post-dose	47	58		
1: Deterioration in night-time symptoms	2	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Visit 3

Adverse event reporting additional description:

There were no deaths, other SAEs in this study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Gaviscon Advance
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Reporting group description:

Gaviscon Advance 10 ml taken 4 times a day for 7 days.

Reporting group title	Placebo
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Reporting group description:

Placebo 10 ml taken 4 times a day for 7 days.

Serious adverse events	Gaviscon Advance	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 66 (0.00%)	0 / 70 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Gaviscon Advance	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 66 (24.24%)	17 / 70 (24.29%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 66 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	1 / 66 (1.52%)	1 / 70 (1.43%)	
occurrences (all)	1	1	
Surgical and medical procedures			

Therapy change subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 4	0 / 70 (0.00%) 0	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 70 (1.43%) 2	
Headache subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4	3 / 70 (4.29%) 3	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 70 (1.43%) 1	
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 70 (1.43%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	1 / 70 (1.43%) 1	
Constipation subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	0 / 70 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2	1 / 70 (1.43%) 1	
Dyspepsia subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2	0 / 70 (0.00%) 0	
Haemorrhoids thrombosed subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 70 (1.43%) 1	
Hypoaesthesia oral subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	0 / 70 (0.00%) 0	

Nausea subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3	6 / 70 (8.57%) 6	
Vomiting subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 70 (1.43%) 1	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	0 / 70 (0.00%) 0	
Epistaxis subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	0 / 70 (0.00%) 0	
Infections and infestations Influenza subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	2 / 70 (2.86%) 2	
Pharyngitis subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 70 (1.43%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2012	1. Clarification of ambiguities in the inclusion criteria 2. Change to SAE reporting procedures according to latest RB SOP 3. Increase in the number of potential sites in Denmark 4. Set up of sites in Germany
14 November 2012	1. Clarification of ambiguities in the inclusion/exclusion criteria at the request of the German CA (BfArM) and the German leading EC. 2. Change in the procedure for reporting incorrect dosing and pregnancy in accordance with the latest RB protocol template (which complied with regulatory requirements).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported