



Clinical trial results:

An investigator-blinded, active-controlled phase 3 study to prove the non-inferior efficacy of a Clotrimazole ovule (500 mg) versus a Clotrimazole vaginal tablet (500 mg) in vaginal candidiasis

Summary

EudraCT number	2008-000718-63
Trial protocol	DE
Global end of trial date	27 May 2009

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	13071
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00755053
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee , Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 May 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferior efficacy of a single dose of clotrimazole 500 milligram (mg) vaginal ovule compared to a single dose of clotrimazole 500 mg vaginal tablet at visit 2 (10-14 days post-application), in terms of overall response defined as clinical cure and mycological cure.

Protection of trial subjects:

All clinical work conducted in this study was subjected to the rules of Good Clinical Practice (GCP) and under the guidelines of Declaration of Helsinki. These practices include the following areas: Institutional review board (IRB)/Independent Ethics Committee procedures, informed consent, protocol adherence, administrative documents, drug supply accountability, data collection, subject records (source documents), adverse event (AE) recording and reporting, inspection and records retention. The subjects' records were kept confidential and were insured by the sponsor.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2008
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	Germany: 240
Country: Number of subjects enrolled	Russian Federation: 225
Worldwide total number of subjects	465
EEA total number of subjects	240

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)	16
Adults (18-64 years)	449

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted between 18 September 2008 and 27 May 2009 at 18 centers from 2 countries; Germany (11 centers) and Russia (7 centers).

Pre-assignment

Screening details:

At screening/baseline, clinical symptoms (itching, burning/irritation, discharge, dysuria) and signs (vaginal edema, erythema and excoriation, and vulval edema, erythema and excoriation) of vaginitis were assessed and a mycological testing was performed.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator ^[1]

Blinding implementation details:

Packages distributed to the subjects were not distinguished by the investigator. Only the randomization code for each subject was supplied to each investigator in sealed envelopes. The code was kept in a secure place at the study sites and at the sponsor. The code was only to be broken in case of an emergency. Once all data had been quality controlled and the data were accepted for final analysis after the blind data meeting, the database was locked and the randomization code was broken.

Arms

Are arms mutually exclusive?	Yes
Arm title	Clotrimazole tablet (Canesten, BAY-B5097)

Arm description:

Single intravaginal dose of 500 mg clotrimazole tablet at Visit 1 (Day 0).

Arm type	Active comparator
Investigational medicinal product name	Clotrimazole
Investigational medicinal product code	BAY-B5097
Other name	Canesten
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Single intravaginal dose of 500 mg clotrimazole tablet at Visit 1 (Day 0).

Arm title	Clotrimazole ovule (Canesten, BAY-B5097)
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Arm description:

Single intravaginal dose of 500 mg clotrimazole ovule at Visit 1 (Day 0).

Arm type	Experimental
Investigational medicinal product name	Clotrimazole
Investigational medicinal product code	BAY-B5097
Other name	Canesten
Pharmaceutical forms	Suppository
Routes of administration	Vaginal use

Dosage and administration details:

Single intravaginal dose of 500 mg clotrimazole ovule at Visit 1 (Day 0).

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Study medication could not be blinded, therefore an investigator-blinded design was

chosen in order not to bias the clinical evaluation of symptoms and signs.

Number of subjects in period 1 ^[2]	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)
Started	228	235
Completed	228	235

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Not all the enrolled subjects were treated with study drugs. As baseline only included treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator ^[3]

Blinding implementation details:

Packages distributed to the subjects were not distinguished by the investigator. Only the randomization code for each subject was supplied to each investigator in sealed envelopes. The code was kept in a secure place at the study sites and at the sponsor. The code was only to be broken in case of an emergency. Once all data had been quality controlled and the data were accepted for final analysis after the blind data meeting, the database was locked and the randomization code was broken.

Arms

Are arms mutually exclusive?	No
Arm title	Clotrimazole tablet (Canesten, BAY-B5097)

Arm description:

Single intravaginal dose of 500 mg clotrimazole tablet at Visit 1 (Day 0).

Arm type	Active comparator
Investigational medicinal product name	Clotrimazole
Investigational medicinal product code	BAY-B5097
Other name	Canesten
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Single intravaginal dose of 500 mg clotrimazole tablet at Visit 1 (Day 0).

Arm title	Clotrimazole ovule (Canesten, BAY-B5097)
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Arm description:

Single intravaginal dose of 500 mg clotrimazole ovule at Visit 1 (Day 0).

Arm type	Experimental
Investigational medicinal product name	Clotrimazole
Investigational medicinal product code	BAY-B5097
Other name	Canesten
Pharmaceutical forms	Suppository
Routes of administration	Vaginal use

Dosage and administration details:

Single intravaginal dose of 500 mg clotrimazole ovule at Visit 1 (Day 0).

Notes:

[3] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Study medication could not be blinded, therefore an investigator-blinded design was chosen in order not to bias the clinical evaluation of symptoms and signs.

Number of subjects in period 2	Clotrimazole tablet (Canesten, BAY- B5097)	Clotrimazole ovule (Canesten, BAY- B5097)
Started	228	237
Treated	228	235
Completed	176	172
Not completed	52	65
Adverse event, non-fatal	3	3
Diagnosis of candidiasis not confirmed	33	45
Other-Unspecified	7	6
Lost to follow-up	8	6
Protocol deviation	1	5

Baseline characteristics

Reporting groups

Reporting group title	Clotrimazole tablet (Canesten, BAY-B5097)
Reporting group description: Single intravaginal dose of 500 mg clotrimazole tablet at Visit 1 (Day 0).	
Reporting group title	Clotrimazole ovule (Canesten, BAY-B5097)
Reporting group description: Single intravaginal dose of 500 mg clotrimazole ovule at Visit 1 (Day 0).	

Reporting group values	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)	Total
Number of subjects	228	235	463
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	8	8	16
Adults (18-64 years)	220	227	447
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	31.7	30.5	
standard deviation	± 8.5	± 8	-
Gender categorical Units: Subjects			
Female	228	235	463
Male	0	0	0

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received a dose of the trial medication.	
Subject analysis set title	Intent-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who completed the treatment and at least visit 2 (10-14 days post-application) with a positive mycological test result for Candida at baseline.	
Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description: All subjects who completed the treatment and at least visit 2 (10-14 days post-application), with a	

positive mycological test result for Candida at baseline but without a major protocol violations.

Reporting group values	Safety population	Intent-to-treat population	Per-protocol population
Number of subjects	463	377	366
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	16	14	14
Adults (18-64 years)	447	363	352
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	31.1	31.4	31.4
standard deviation	± 8.3	± 8.3	± 8.3
Gender categorical Units: Subjects			
Female	463	377	366
Male	0	0	0

End points

End points reporting groups

Reporting group title	Clotrimazole tablet (Canesten, BAY-B5097)
Reporting group description: Single intravaginal dose of 500 mg clotrimazole tablet at Visit 1 (Day 0).	
Reporting group title	Clotrimazole ovule (Canesten, BAY-B5097)
Reporting group description: Single intravaginal dose of 500 mg clotrimazole ovule at Visit 1 (Day 0).	
Reporting group title	Clotrimazole tablet (Canesten, BAY-B5097)
Reporting group description: Single intravaginal dose of 500 mg clotrimazole tablet at Visit 1 (Day 0).	
Reporting group title	Clotrimazole ovule (Canesten, BAY-B5097)
Reporting group description: Single intravaginal dose of 500 mg clotrimazole ovule at Visit 1 (Day 0).	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received a dose of the trial medication.	
Subject analysis set title	Intent-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who completed the treatment and at least visit 2 (10-14 days post-application) with a positive mycological test result for Candida at baseline.	
Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description: All subjects who completed the treatment and at least visit 2 (10-14 days post-application), with a positive mycological test result for Candida at baseline but without a major protocol violations.	

Primary: Percentage of Subjects With Overall Response at Visit 2 (Day 10 to 14)

End point title	Percentage of Subjects With Overall Response at Visit 2 (Day 10 to 14)
End point description: Overall response was defined as clinical cure and mycological cure. Mycological cure was defined as negative microscopy and negative mycological culture and a clinical cure was defined as absence of the symptoms itching and burning/ irritation, and no more than mild expressions of other symptoms and signs, and no worsening of any symptoms and signs compared to the baseline visit.	
End point type	Primary
End point timeframe: Day 10 up to 14	

End point values	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186 ^[1]	180 ^[2]		
Units: Percentage of subjects				
number (confidence interval 95%)	66.1 (59.1 to	73.3 (66.6 to		

Notes:

[1] - Per-Protocol population was used for analysis.

[2] - Per-Protocol population was used for analysis.

Statistical analyses

Statistical analysis title	Ovule versus Tablet
Statistical analysis description:	
Difference in treatment groups was expressed as percentage along with 95% Confidence Interval (CI).	
Comparison groups	Clotrimazole tablet (Canesten, BAY-B5097) v Clotrimazole ovule (Canesten, BAY-B5097)
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.33
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	21.7

Secondary: Percentage of Subjects With Overall Response at Visit 3 (Week 6 to 8)

End point title	Percentage of Subjects With Overall Response at Visit 3 (Week 6 to 8)
End point description:	
Overall response was defined as clinical cure and mycological cure, mycological cure was defined as negative microscopy and negative mycological culture and a clinical cure was defined as absence of the symptoms itching and burning/ irritation, and no more than mild expressions of other symptoms and signs, and no worsening of any symptoms and signs compared to the baseline visit.	
End point type	Secondary
End point timeframe:	
Week 6 up to 8	

End point values	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169 ^[3]	169 ^[4]		
Units: percentage of subjects				
number (confidence interval 95%)	75.7 (69 to 82.5)	73.4 (66.4 to 80.3)		

Notes:

[3] - Per Protocol Population with available data only, was used for analysis.

[4] - Per Protocol Population with available data only, was used for analysis.

Statistical analyses

Statistical analysis title	Ovule versus Tablet
Statistical analysis description: Difference in treatment groups was expressed as percentage along with 95% CI.	
Comparison groups	Clotrimazole ovule (Canesten, BAY-B5097) v Clotrimazole tablet (Canesten, BAY-B5097)
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.75
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	12.2

Secondary: Percentage of Subjects With Clinical Cure at Visit 2 (Day 10 to 14)

End point title	Percentage of Subjects With Clinical Cure at Visit 2 (Day 10 to 14)
End point description: Subjects with clinical cure (resolution of signs and symptoms of vaginitis) at Visit 2 (Day 10 to 14) by signs of vaginitis (vaginal edema, erythema and excoriation, and vulval edema, erythema and excoriation), symptoms of vaginitis (itching, burning/irritation, discharge, dysuria) and both signs and symptoms of vaginitis.	
End point type	Secondary
End point timeframe: Day 10 up to 14	

End point values	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186 ^[5]	180 ^[6]		
Units: percentage of subjects				
number (confidence interval 95%)				
Clinical Symptoms	84.9 (79.5 to 90.4)	88.9 (84 to 93.8)		

Clinical Signs	97.3 (94.7 to 99.9)	98.9 (97.1 to 100.7)		
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Notes:

[5] - Per Protocol Population with available data only, was used for analysis.

[6] - Per Protocol Population with available data only, was used for analysis.

Statistical analyses

Statistical analysis title	Ovule versus tablet for clinical symptoms
Statistical analysis description:	
Difference in treatment groups was expressed as percentage along with 95% CI.	
Comparison groups	Clotrimazole tablet (Canesten, BAY-B5097) v Clotrimazole ovule (Canesten, BAY-B5097)
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage difference
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	15.9

Statistical analysis title	Ovule versus tablet for signs of vaginitis
Statistical analysis description:	
Difference in treatment groups was expressed as percentage along with 95% CI.	
Comparison groups	Clotrimazole tablet (Canesten, BAY-B5097) v Clotrimazole ovule (Canesten, BAY-B5097)
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	9.4

Secondary: Percentage of Subjects With Clinical Cure at Visit 3 (Week 6 to 8)

End point title	Percentage of Subjects With Clinical Cure at Visit 3 (Week 6 to 8)
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End point description:

Subjects with clinical cure (resolution of signs and symptoms of vaginitis) at Visit 2 (Day 10 to 14) by signs of vaginitis (vaginal edema, erythema and excoriation, and vulval edema, erythema and excoriation), symptoms of vaginitis (itching, burning/irritation, discharge, dysuria) and both signs and symptoms of vaginitis.

End point type	Secondary
End point timeframe:	
Week 6 up to 8	

End point values	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170 ^[7]	170 ^[8]		
Units: percentage of subjects				
number (confidence interval 95%)				
Clinical Symptoms	93.5 (89.5 to 97.5)	92.9 (88.8 to 97.1)		
Clinical Signs	98.8 (96.9 to 100.7)	95.3 (91.8 to 98.8)		

Notes:

[7] - Per Protocol Population with available data only, was used for analysis.

[8] - Per Protocol Population with available data only, was used for analysis.

Statistical analyses

Statistical analysis title	Ovule versus tablet for clinical symptoms
Statistical analysis description:	
Difference in treatment groups was expressed as percentage along with 95% CI.	
Comparison groups	Clotrimazole tablet (Canesten, BAY-B5097) v Clotrimazole ovule (Canesten, BAY-B5097)
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	10.1

Statistical analysis title	Ovule versus tablet for signs of vaginitis
Statistical analysis description:	
Difference in treatment groups was expressed as percentage along with 95% CI.	
Comparison groups	Clotrimazole tablet (Canesten, BAY-B5097) v Clotrimazole ovule (Canesten, BAY-B5097)

Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2
upper limit	5.2

Secondary: Percentage of Subjects With Mycological Cure at Visit 2 (Day 10 to 14)

End point title	Percentage of Subjects With Mycological Cure at Visit 2 (Day 10 to 14)
End point description:	Subjects with mycological cure (negative microscopy and negative culture) of Candida spp. at Visit 2 (Day 10 to 14) were reported.
End point type	Secondary
End point timeframe:	Day 10 up to 14

End point values	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186 ^[9]	180 ^[10]		
Units: percentage of subjects				
number (confidence interval 95%)	78.5 (72.3 to 84.7)	81.7 (75.7 to 87.6)		

Notes:

[9] - Per Protocol Population with available data only, was used for analysis.

[10] - Per Protocol Population with available data only, was used for analysis.

Statistical analyses

Statistical analysis title	Ovule versus tablet
Statistical analysis description:	Difference in treatment groups was expressed as percentage along with 95% CI.
Comparison groups	Clotrimazole ovule (Canesten, BAY-B5097) v Clotrimazole tablet (Canesten, BAY-B5097)
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage difference
Point estimate	3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	16.5

Secondary: Percentage of Subjects With Mycological Cure at Visit 3 (Week 6 to 8)

End point title	Percentage of Subjects With Mycological Cure at Visit 3 (Week 6 to 8)
End point description: Subjects with mycological cure (negative microscopy and negative culture) of Candida spp. at Visit 3 (Week 6 to 8).	
End point type	Secondary
End point timeframe: Week 6 to 8	

End point values	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170 ^[11]	169 ^[12]		
Units: percentage of subjects				
number (confidence interval 95%)	81.8 (75.7 to 87.9)	78.1 (71.6 to 84.6)		

Notes:

[11] - Per Protocol Population with available data only, was used for analysis.

[12] - Per Protocol Population with available data only, was used for analysis.

Statistical analyses

Statistical analysis title	Ovule versus tablet
Statistical analysis description: Difference in treatment groups was expressed as percentage along with 95% CI.	
Comparison groups	Clotrimazole tablet (Canesten, BAY-B5097) v Clotrimazole ovule (Canesten, BAY-B5097)
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage difference
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	10.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline (Day 0) up to the end of study (Day 60).

Adverse event reporting additional description:

Treatment-emergent adverse events were defined as adverse events/serious adverse events that started or worsened after the study drug treatment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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Reporting groups

Reporting group title	Clotrimazole tablet (Canesten, BAY-B5097)
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Reporting group description:

Single intravaginal dose of 500 mg clotrimazole tablet at Visit 1 (Day 0).

Reporting group title	Clotrimazole ovule (Canesten, BAY-B5097)
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Reporting group description:

Single intravaginal dose of 500 mg clotrimazole ovule at Visit 1 (Day 0)

Serious adverse events	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 228 (0.00%)	0 / 235 (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	Clotrimazole tablet (Canesten, BAY-B5097)	Clotrimazole ovule (Canesten, BAY-B5097)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 228 (7.89%)	17 / 235 (7.23%)	
Cardiac disorders			
Tachycardia paroxysmal			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	0 / 228 (0.00%) 0	4 / 235 (1.70%) 4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 228 (2.19%)	3 / 235 (1.28%)	
occurrences (all)	6	3	
Abdominal pain lower			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 228 (0.44%)	1 / 235 (0.43%)	
occurrences (all)	1	1	
Toothache			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Dyspareunia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	1	0	
Metrorrhagia			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	0	1	
Uterine cervical erosion			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	1	0	
Vaginal haemorrhage			

subjects affected / exposed occurrences (all)	2 / 228 (0.88%) 3	0 / 235 (0.00%) 0	
Vulvovaginal discomfort subjects affected / exposed occurrences (all)	0 / 228 (0.00%) 0	1 / 235 (0.43%) 1	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 228 (0.44%) 1	2 / 235 (0.85%) 2	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 228 (0.00%) 0	2 / 235 (0.85%) 3	
Infections and infestations Acute tonsillitis subjects affected / exposed occurrences (all)	0 / 228 (0.00%) 0	1 / 235 (0.43%) 1	
Bronchitis subjects affected / exposed occurrences (all)	1 / 228 (0.44%) 1	0 / 235 (0.00%) 0	
Cystitis subjects affected / exposed occurrences (all)	1 / 228 (0.44%) 1	0 / 235 (0.00%) 0	
Furuncle subjects affected / exposed occurrences (all)	1 / 228 (0.44%) 1	0 / 235 (0.00%) 0	
Laryngitis subjects affected / exposed occurrences (all)	0 / 228 (0.00%) 0	1 / 235 (0.43%) 1	
Mycoplasma infection subjects affected / exposed occurrences (all)	1 / 228 (0.44%) 1	0 / 235 (0.00%) 0	
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 228 (0.44%) 1	0 / 235 (0.00%) 0	
Rhinitis			

subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	0	1	
Trichomoniasis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2008	Change of exclusion criteria due to harmonization with the summary of product characteristics and change of the microbiological methods to more specific procedures as utilized in the involved labs at Berlin and Moscow.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported