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Trial record **1 of 2** for: 100A2303

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Study to Evaluate the Efficacy and Safety of Combination Aliskiren/Amlodipine in Patients Not Adequately Responding to Aliskiren Alone

This study has been completed.

Sponsor:
Novartis

Information provided by:
Novartis

ClinicalTrials.gov Identifier:
NCT00777946

First received: October 20, 2008
Last updated: June 30, 2011
Last verified: June 2011
History of Changes

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Results First Received: December 13, 2010

Study Type:	Interventional
Study Design:	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
Condition:	Hypertension
Interventions:	Drug: Aliskiren 300 mg Drug: Aliskiren/Amlodipine 300/5 mg Drug: Aliskiren/Amlodipine 300/10 mg Drug: Placebo to Aliskiren Drug: Placebo to Aliskiren/Amlodipine

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
This study consisted of a 7 day wash-out period and a 4 week single-blind run-in period prior to the 8 week double-blind period. 2 of the 820 randomized patients were randomized in error, are not included in the 818 participants enrolled in the double-blind period, did not receive study drug & are not included in the Safety and Full Analysis Sets.

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.

Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Participant Flow: Overall Study

	Aliskiren 300 mg/Amlodipine 10 mg	Aliskiren 300 mg/Amlodipine 5 mg	Aliskiren 300 mg
STARTED	283 [1]	277 [2]	260
Safety & Full Analysis Sets	282	276	260
COMPLETED	262	271	244
NOT COMPLETED	21	6	16
Adverse Event	11	1	3
Lack of Efficacy	0	0	9
Condition no longer required study drug	1	0	0
Patient withdrew consent	3	2	3
Lost to Follow-up	3	1	0
Protocol deviation	2	1	1
Randomized in error	1	1	0

[1] 1 patient in the Aliskiren 300 mg/Amlodipine 10 mg group was randomized in error.
[2] 1 patient in the Aliskiren 300 mg/Amlodipine 5 mg group was randomized in error.

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.
Total	Total of all reporting groups

Baseline Measures

	Aliskiren 300 mg/Amlodipine 10 mg	Aliskiren 300 mg/Amlodipine 5 mg	Aliskiren 300 mg	Total
Number of Participants [units: participants]	283	277	260	820
Age [units: years] Mean (Standard Deviation)	54.6 (10.67)	54.4 (10.69)	54.7 (10.99)	54.6 (10.77)

Gender [units: participants]				
Female	**120**	**101**	**103**	**324**
Male	**163**	**176**	**157**	**496**

Outcome Measures

Hide All Outcome Measures

1. Primary: Change From Baseline to End of Study in the Mean Sitting Diastolic Blood Pressure (msDBP) [Time Frame: Baseline, End of Study (Week 8)]

Measure Type	Primary
Measure Title	Change From Baseline to End of Study in the Mean Sitting Diastolic Blood Pressure (msDBP)
Measure Description	After the patient had been sitting for 5 minutes, systolic and diastolic blood pressures were measured 3 times using the automatic Blood Pressure monitor and appropriate size cuff. The repeat sitting measurements were made at 1-2 minute intervals and the mean of these 3 sitting blood pressure measurements was used as the average sitting blood pressure for that visit. The difference of the msDBP at baseline from the msDBP at 8 weeks was calculated using an Analysis of Covariance (ANCOVA) model with baseline as a covariate and treatment and region as two factors.
Time Frame	Baseline, End of Study (Week 8)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Full Analysis Set (all randomized patients who received study drug). Three patients (1 in Aliskiren 300 mg/Amlodipine 10 mg group and 2 in the Aliskiren 300 mg/Amlodipine 5 mg group were excluded from the analysis due to lack of post-baseline assessment.

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Measured Values

	Aliskiren 300 mg/Amlodipine 10 mg	**Aliskiren 300 mg/Amlodipine 5 mg**	**Aliskiren 300 mg**
Number of Participants Analyzed [units: participants]	**281**	**274**	**260**
Change From Baseline to End of Study in the Mean Sitting Diastolic Blood Pressure (msDBP) [units: mm Hg] Least Squares Mean (Standard Error)	**-13.07 (0.463)**	**-10.54 (0.467)**	**-5.84 (0.480)**

No statistical analysis provided for Change From Baseline to End of Study in the Mean Sitting Diastolic Blood Pressure (msDBP)

2. Secondary: Change From Baseline to End of Study in the Mean Sitting Systolic Blood Pressure (msSBP) [Time Frame: Baseline, End of

Study (Week 8)]

Measure Type	Secondary
Measure Title	Change From Baseline to End of Study in the Mean Sitting Systolic Blood Pressure (msSBP)
Measure Description	After the patient had been sitting for 5 minutes, systolic and diastolic blood pressures were measured 3 times using the automatic Blood Pressure monitor and appropriate size cuff. The repeat sitting measurements were made at 1-2 minute intervals and the mean of these 3 sitting blood pressure measurements was used as the average sitting blood pressure for that visit. The difference of the msSBP at baseline from the msSBP at 8 weeks was calculated using an ANCOVA model with baseline as a covariate and treatment and region as two factors.
Time Frame	Baseline, End of Study (Week 8)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Full Analysis Set (all randomized patients who received study drug). Three patients (1 in Aliskiren 300 mg/Amlodipine 10 mg group and 2 in the Aliskiren 300 mg/Amlodipine 5 mg group were excluded from the analysis due to lack of post-baseline assessment.

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Measured Values

	Aliskiren 300 mg/Amlodipine 10 mg	**Aliskiren 300 mg/Amlodipine 5 mg**	**Aliskiren 300 mg**
Number of Participants Analyzed [units: participants]	**281**	**274**	**260**
Change From Baseline to End of Study in the Mean Sitting Systolic Blood Pressure (msSBP) [units: mm Hg] Least Squares Mean (Standard Error)	**-18.04 (0.780)**	**-14.43 (0.788)**	**-6.42 (0.809)**

No statistical analysis provided for Change From Baseline to End of Study in the Mean Sitting Systolic Blood Pressure (msSBP)

3. Secondary: Number of Participants With Serious Adverse Events and Adverse Events [Time Frame: 8 weeks]

Measure Type	Secondary
Measure Title	Number of Participants With Serious Adverse Events and Adverse Events
Measure Description	The number of participants with any Serious Adverse Event and the number of participants with Adverse Events in any system organ class. Additional information about Adverse Events can be found in the Adverse Event Section.
Time Frame	8 weeks
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Safety Population consisted of all randomized participants who received study drug.

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Measured Values

	Aliskiren 300 mg/Amlodipine 10 mg	**Aliskiren 300 mg/Amlodipine 5 mg**	**Aliskiren 300 mg**
Number of Participants Analyzed [units: participants]	**282**	**276**	**260**
Number of Participants With Serious Adverse Events and Adverse Events [units: participants]			
Serious Adverse Events	**3**	**4**	**1**
Adverse Events	**85**	**80**	**59**

No statistical analysis provided for Number of Participants With Serious Adverse Events and Adverse Events

4. Secondary: Percentage of Participants Achieving Blood Pressure Control [Time Frame: 8 weeks]

Measure Type	Secondary
Measure Title	Percentage of Participants Achieving Blood Pressure Control
Measure Description	After the patient had been sitting for 5 minutes, with the back supported and both feet placed on the floor, systolic and diastolic blood pressures were measured 3 times using the automatic Blood Pressure monitor and appropriate size cuff. The repeat sitting measurements were made at 1-2 minute intervals and the mean of these 3 sitting blood pressure measurements was used as the average sitting blood pressure for that visit. Blood Pressure control was defined as having a mean sitting Diastolic Blood Pressure <90 and a mean sitting Systolic Blood Pressure <140.
Time Frame	8 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Full Analysis Set (all randomized patients who received study drug). Three patients (1 in Aliskiren 300 mg/Amlodipine 10 mg group and 2 in the Aliskiren 300 mg/Amlodipine 5 mg group were excluded from the analysis due to lack of post-baseline assessment.

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily

	in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Measured Values

	Aliskiren 300 mg/Amlodipine 10 mg	Aliskiren 300 mg/Amlodipine 5 mg	Aliskiren 300 mg
Number of Participants Analyzed [units: participants]	**281**	**274**	**260**
Percentage of Participants Achieving Blood Pressure Control [units: Percentage of participants]	**65.5**	**56.5**	**31.5**

No statistical analysis provided for Percentage of Participants Achieving Blood Pressure Control

5. Secondary: Percentage of Participants Achieving a Diastolic Blood Pressure Response [Time Frame: 8 weeks]

Measure Type	Secondary
Measure Title	Percentage of Participants Achieving a Diastolic Blood Pressure Response
Measure Description	After the patient had been sitting for 5 minutes, with the back supported and both feet placed on the floor, systolic and diastolic blood pressures were measured 3 times using the automatic Blood Pressure monitor and appropriate size cuff. The repeat sitting measurements were made at 1-2 minute intervals and the mean of these 3 sitting blood pressure measurements was used as the average sitting blood pressure for that visit. A Diastolic Blood Pressure Response was defined as a mean sitting Diastolic Blood Pressure (msDBP) <90 mmHg or a ≥ 10 mmHg reduction in msDBP from baseline.
Time Frame	8 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Full Analysis Set (all randomized patients who received study drug). Three patients (1 in Aliskiren 300 mg/Amlodipine 10 mg group and 2 in the Aliskiren 300 mg/Amlodipine 5 mg group were excluded from the analysis due to lack of post-baseline assessment.

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Measured Values

	Aliskiren 300 mg/Amlodipine 10 mg	Aliskiren 300 mg/Amlodipine 5 mg	Aliskiren 300 mg
Number of Participants Analyzed [units: participants]	**281**	**274**	**260**

Percentage of Participants Achieving a Diastolic Blood Pressure Response [units: Percentage of participants]	**83.6**	**77.7**	**51.5**

No statistical analysis provided for Percentage of Participants Achieving a Diastolic Blood Pressure Response

6. Secondary: Percentage of Participants Achieving a Systolic Blood Pressure Response [Time Frame: 8 weeks]

Measure Type	Secondary
Measure Title	Percentage of Participants Achieving a Systolic Blood Pressure Response
Measure Description	After the patient had been sitting for 5 minutes, with the back supported and both feet placed on the floor, systolic and diastolic blood pressures were measured 3 times using the automatic Blood Pressure monitor and appropriate size cuff. The repeat sitting measurements were made at 1-2 minute intervals and the mean of these 3 sitting blood pressure measurements was used as the average sitting blood pressure for that visit. A Systolic Blood Pressure Response was defined as a mean sitting Systolic Blood Pressure (msSBP) <140 mmHg or a ≥ 20 mmHg reduction in msSBP from baseline.
Time Frame	8 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Full Analysis Set (all randomized patients who received study drug). Three patients (1 in Aliskiren 300 mg/Amlodipine 10 mg group and 2 in the Aliskiren 300 mg/Amlodipine 5 mg group were excluded from the analysis due to lack of post-baseline assessment.

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Measured Values

	Aliskiren 300 mg/Amlodipine 10 mg	**Aliskiren 300 mg/Amlodipine 5 mg**	**Aliskiren 300 mg**
Number of Participants Analyzed [units: participants]	**281**	**274**	**260**
Percentage of Participants Achieving a Systolic Blood Pressure Response [units: Percentage of participants]	**77.2**	**69.7**	**43.8**

No statistical analysis provided for Percentage of Participants Achieving a Systolic Blood Pressure Response

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	8 weeks
Additional Description	Safety set (all patients who received at least 1 dose of double-blind study drug).

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Serious Adverse Events

	Aliskiren 300 mg/Amlodipine 10 mg	Aliskiren 300 mg/Amlodipine 5 mg	Aliskiren 300 mg
Total, serious adverse events			
# participants affected / at risk	**3/282 (1.06%)**	**4/276 (1.45%)**	**1/260 (0.38%)**
Ear and labyrinth disorders			
Vertigo † 1			
# participants affected / at risk	**0/282 (0.00%)**	**1/276 (0.36%)**	**0/260 (0.00%)**
General disorders			
Pyrexia † 1			
# participants affected / at risk	**0/282 (0.00%)**	**1/276 (0.36%)**	**0/260 (0.00%)**
Immune system disorders			
Drug hypersensitivity † 1			
# participants affected / at risk	**1/282 (0.35%)**	**0/276 (0.00%)**	**0/260 (0.00%)**
Infections and infestations			
Lobar pneumonia † 1			
# participants affected / at risk	**1/282 (0.35%)**	**0/276 (0.00%)**	**0/260 (0.00%)**
Viral infection † 1			
# participants affected / at risk	**0/282 (0.00%)**	**1/276 (0.36%)**	**0/260 (0.00%)**
Injury, poisoning and procedural complications			
Post-traumatic pain † 1			
# participants affected / at risk	**0/282 (0.00%)**	**0/276 (0.00%)**	**1/260 (0.38%)**
Road traffic accident † 1			
# participants affected / at risk	**0/282 (0.00%)**	**0/276 (0.00%)**	**1/260 (0.38%)**
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion † 1			
# participants affected / at risk	**1/282 (0.35%)**	**0/276 (0.00%)**	**0/260 (0.00%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant † 1			
# participants affected / at risk	**0/282 (0.00%)**	**1/276 (0.36%)**	**0/260 (0.00%)**
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease † 1			

# participants affected / at risk	0/282 (0.00%)	1/276 (0.36%)	0/260 (0.00%)

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA

Other Adverse Events

Hide Other Adverse Events

Time Frame	8 weeks
Additional Description	Safety set (all patients who received at least 1 dose of double-blind study drug).

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Aliskiren 300 mg/Amlodipine 10 mg	Participants received 1 Aliskiren/Amlodipine 300/10mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg/Amlodipine 5 mg	Participants received 1 Aliskiren/Amlodipine 300/5mg tablet + 1 Placebo to Aliskiren tablet once daily in the morning for 8 weeks.
Aliskiren 300 mg	Participants received 1 Aliskiren 300 mg tablet + 1 Placebo to Aliskiren/Amlodipine tablet orally once daily in the morning for 8 weeks.

Other Adverse Events

	Aliskiren 300 mg/Amlodipine 10 mg	Aliskiren 300 mg/Amlodipine 5 mg	Aliskiren 300 mg
Total, other (not including serious) adverse events			
# participants affected / at risk	**26/282 (9.22%)**	**6/276 (2.17%)**	**1/260 (0.38%)**
General disorders			
Oedema peripheral † 1			
# participants affected / at risk	**26/282 (9.22%)**	**6/276 (2.17%)**	**1/260 (0.38%)**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.
There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial

results after the trial is completed.

The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

☑ **Restriction Description:** The terms and conditions of Novartis' agreements with its investigators may vary. However, Novartis does not prohibit any investigator from publishing. Any publications from a single-site are postponed until the publication of the pooled data (i.e., data from all sites) in the clinical trial.

Results Point of Contact:

Name/Title: Study Director
Organization: Novartis Pharmaceuticals
phone: 862-778-8300

No publications provided by Novartis

Publications automatically indexed to this study:

Glorioso N, Thomas M, Troffa C, Argiolas G, Patel S, Baek I, Zhang J. Antihypertensive efficacy and tolerability of aliskiren/amlodipine single- pill combinations in patients with an inadequate response to aliskiren monotherapy. Curr Vasc Pharmacol. 2012 Nov;10(6):748-55.

Responsible Party:	External Affairs, Novartis
ClinicalTrials.gov Identifier:	NCT00777946 History of Changes
Other Study ID Numbers:	CSPA**100A2303**
Study First Received:	October 20, 2008
Results First Received:	December 13, 2010
Last Updated:	June 30, 2011
Health Authority:	Estonia: The State Agency of Medicine France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Iceland: Icelandic Medicines Control Agency India: Ministry of Health Italy: The Italian Medicines Agency Lithuania: State Medicine Control Agency - Ministry of Health South Africa: Medicines Control Council South Korea: Korea Food and Drug Administration (KFDA) Spain: Spanish Agency of Medicines Venezuela: Ministry of Health and Social Development