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Committee for Medicinal Products for Human Use (CHMP)

Stocrin

(efavirenz)

Procedure No. EMEA/H/C/000250/A45/56

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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Rapporteur's Assessment Report for Post-Authorisation Commitments (PACs)

P45 056

Stocrin (efavirenz)

EMEA/H/C/250

Marketing Authorisation Holder: Merck Sharp & Dohme

Rapporteur:	Prof. Beatriz Silva Lima
Start of the procedure:	26-04-2009
Date of the report:	02-06-2009
Deadline for CHMP member's comments:	09-06-2009
Date of the updated report (if applicable):	
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I. ASSESSMENT

Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:
Fulfilment of the CHMP's request to provide all existing data/information on the paediatric studies listed in a previous submission made under article 45of the Regulation 1901/2006, as amended, concerning the study MK-0831, Protocol 908: paediatric Expanded Access Program – Oral Solution.

Assessment

Study 908 (A Noncomparative, Open, Multisite study to Monitor the Safety and Tolerability of Efavirenz Oral Solution Given in Combination Antiretroviral Therapy (ART) in ART-naïve or - experienced HIV-1 Infected Patients Age 3 to 16 Years Who Have Failed Therapy or Are Intolerant to Their Current ART Regimen.) was a noncomparative, open, multisite study to monitor the safety and tolerability of efavirenz oral solution given in combination antiretroviral therapy (ART) in ART-naïve or -experienced HIV-1 infected patients age 3 to 16 years who have failed therapy or are intolerant to their current ART regimen.

The primary objectives were to monitor the safety and tolerability of efavirenz oral solution in combination ART for the treatment of HIV-1 infection in ART-naïve or -experienced patients aged 3 to
16 years and weighing at least 10 kg. (22 lb.) who have failed or are intolerant to their current ART regimen, have plasma HIV-1 RNA>400 copies/mL and are able to take liquid medications but have difficulty swallowing capsules.

This Pediatric Expanded Access Program – Oral Solution (PEAP-OS) was anticipated to end when efavirenz oral solution would be approved and reimbursed in participating countries (unless terminated prematurely).
Approximately 150 HIV-1 seropositive pediatric patients were to be enrolled in this PEAP-OS. Patients in this study must be between the age of 3 and 16 years and weighing at least 10 kg (22 lb.). The patients may be ART-naïve or -experienced. Patients must have HIV-1 RNA >400 copies/mL within 30 days of enrollment. Females of childbearing potential must have a negative serum pregnancy test 30 days prior to enrollment and negative urine pregnancy test prior to entry on Day 1. Efavirenz oral solution with concentration of 30 mg/mL will be dosed once daily according to weight (see table below).

Physical examinations (including vital signs and body weight) were to be performed at prestudy (within 30 days prior to treatment) and at every clinic visit after study entry. Laboratory tests for inclusion/exclusion criteria are required to be done at prestudy. Safety laboratory tests of blood and urine are recommended to be done at every clinic visit after study entry. Routine clinic visits will be scheduled at Week 2, 4, and at two month intervals after entry into the study for the first 6 months and at every 3 months for the rest of the duration of the study period to evaluate the status of the patient, drug compliance and to assess serious and study-specific reportable adverse experiences (see Section I.G.1.). A serum pregnancy test will be performed for females of childbearing potential within 30 days prior to entry into the study. Urine pregnancy tests will be performed on entry (Day 1) and at every clinic visit to rule out pregnancy. Patients who become pregnant must discontinue therapy with efavirenz. Additional physical examinations, laboratory tests, and other procedures (e.g., ECG, chest X ray, ophthalmologic examination) will be performed when clinically indicated as determined by the treating physician for the duration of the study.

The study was terminated early and only 5 patients entered the study. Five patients, 3 in Colombia and 2 in Portugal, participated in this study. The characteristics of these patients are listed in Table 1.

Table 1: Patient Demographics

Country	AN	Gender	Age (Yr)	Race	Study Duration (Days)	Height (cm)	Weight (kg)
Colombia	1	Boy	5	Hispanic	147	122	21.5
Colombia	2	Boy	11	Hispanic	127	129	24.5
Colombia	3	Girl	4	Hispanic	98	102	16.5
Portugal	3001	Girl	3	White	531	93	16.7
Portugal	3003	Boy	5	White	4	113	19.8

Four patients continued in the study till completion or trial termination at investigational site. One patient (AN 3003) discontinued due to a clinical AE (parotitis).

Safety results

Patient safety was assessed by the collection of serious and study-specific adverse events. Serious and study-specific adverse events were reported for 3 patients in the study. All these adverse events are listed in Table 2. One patient (AN 2) had a probably drug-related adverse event of exanthem. This adverse event was not serious and no action was taken with respect to the study drug. One patient had a serious adverse event of parotitis. The patient was hospitalized and discontinued from study drug. The adverse event was definitely not drug-related following the investigator assessment.

Table 2: Listing of Adverse Events

AN	Body system	Adverse Event	Relative Day†	Duration	Serious	Action Taken with respect to Study Drug	Causality
2	Infections and infestations	Otitis media NOS	1	5 Days	No	no action with PRx	def not
	Respiratory, thoracic and mediastinal disorders	Rales	1	3 Days	No	no action with PRx	def not
	Investigations (Laboratory Adverse Event)	AST increased	15	1 Days	No	no action with PRx	def not
	Investigations (Laboratory Adverse Event)	ALT increased	15	1 Days	No	no action with PRx	def not
	Skin and subcutaneous tissue disorders	Rash NOS	1	4.1 Months	No	no action with PRx	def not
	Skin and subcutaneous tissue disorders	Rash maculo-papular	13	7 Days	No	no action with PRx	def not
	Infections and infestations	Oral candidiasis	15	7 Days	No	no action with PRx	def not
	Skin and subcutaneous tissue disorders	Exanthem	13	Continuing	No	no action with PRx	prob
3001	Gastrointestinal disorders	Stomatitis	381	4 Days	No	no action with PRx	prob not
	Gastrointestinal disorders	Diarrhoea NOS	45	27 Days	No	no action with PRx	prob not
3003	Infections and infestations	Parotitis	2	11 Days	Yes	discontinued PRx	def not

† Number of days since start of study at the onset of the adverse event.
PRx: Primary study drug; def: definitely; prob: probably; NOS: Not Otherwise Specified

II. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

The study was prematurely terminated, and all the available data concerning the 5 enrolled subjects was submitted for assessment. These data does not indicate any new reason for concern regarding this formulation of the product. Of note, one of the subjects presented with stomatitis, which may be consistent with the potential for irritation of the oral mucosa which has been described for this formulation.

Overall Conclusion:

☒ PAC fulfilled (all commitments fulfilled) - No further action required