Bristol-Myers Squibb
Bristol-Myers Squibb Pharmaceuticals, Swords, Dublin, Ireland

23rd April 2015

Direct Healthcare Professional Communication

Efavirenz, Sustiva®, Warning about Discontinuation of the Sustiva 30 mg/mL Oral Solution Formulation by the End of October 2015

Dear Healthcare professional,

Bristol-Myers Squibb in agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

Summary

- Commercialisation of the Sustiva 30 mg/mL Oral Solution formulation will be discontinued in Europe by the end of October 2015. Sustiva capsule and tablet availability are not changing. You should plan changes in antiretroviral therapy to avoid a treatment interruption for your patients with human immunodeficiency virus.
- Sustiva can be administered by means of the capsule sprinkle dosing method to paediatric patients and adults unable to swallow intact capsules.
- Switching patients from oral solution to capsule sprinkle method may result in higher drug exposures; therefore, patients should be monitored closely for evidence of Sustiva toxicity during the transition period.

Further information on the safety concern and the recommendations

The decision to discontinue the oral solution was not due to any underlying efficacy or safety concerns regarding this formulation, but rather because of low utilisation and availability of the capsule sprinkle dosing method, which is indicated for a broader range of the paediatric population (greater than 3 months of age and 3.5 kg) as well as for adults unable to swallow intact capsules.

There are important considerations that must be addressed in transitioning a patient from Sustiva Oral Solution to the capsule sprinkle dosing method. Capsule sprinkles offer a more consistent bioavailability across all age groups, including children aged 3 months to 3 years. However, because of the increased bioavailability, higher exposures may result in some individuals when switching from the Oral Solution. The dose should be adjusted according to the prescribing information for the capsules when using the capsule sprinkle method of administration. Patients should be monitored closely for evidence of Sustiva toxicity during the transition period from Oral Solution to capsule sprinkle. While no new toxicities have been identified in patients taking the capsule sprinkle, the potential exists for an increased frequency of known adverse events, particularly in the first few weeks of therapy after the switch. Because young children may not be able to report symptoms

related to toxicity, such as increased irritability, somnolence, and insomnia, close clinical monitoring is warranted.

If a patient develops clinically significant toxicities, substitution of an alternate treatment must be considered.

Further information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Sustiva is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 months of age and older and weighing at least 3.5 kg.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Suspected adverse reactions should be reported to the HPRA using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling (01) 676 4971.

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Any suspected adverse reactions with Sustiva (efavirenz) may also be reported to BMS via telephone at 1 800 749 749 or via email at medical.information@bms.com.

Company contact point

If you have further questions or require additional information, please contact the BMS Medical Information department (telephone: 1 800 749 749; email: medical.information@bms.com):
Bristol-Myers Squibb Pharmaceuticals Limited, BMS House, Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex, UB8 1DH, United Kingdom

Annexes

Relevant sections of the Product Information that have been revised (with changes made visible).

Yours sincerely,

Siobhan Mitchell

Dr Siobhan Mitchell PhD
Medical Director, Ireland
Bristol-Myers Squibb Pharmaceuticals

Bristol-Myers Squibb

Bristol-Myers Squibb Pharmaceuticals, Swords, Dublin, Ireland

SUMMARY OF PRODUCT CHARACTERISTICS

4.1 Therapeutic indications

SUSTIVA is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 ~~years~~ months of age and older and weighing at least 3.5 kg.

4.2 Posology and method of administration

(Note: changes to this section are applicable to the SmPC of the capsule formulation only)

Children and adolescents (3 months to 17 years)

The recommended dose of efavirenz in combination with a PI and/or NRTIs for patients between 3 months and 17 years of age is described in Table 1. Efavirenz intact hard capsules must only be administered to children who are able to reliably swallow hard capsules.

Table 1: Paediatric dose to be administered once daily*

Body Weight kg	efavirenz Dose (mg)	Number of Capsules or Tablets and Strength to Administer
3.5 to < 5	100	one 100 mg capsule
5 to < 7.5	150	one 100 mg capsule + one 50 mg capsule
~~13~~ 7.5 to < 15	200	one 200 mg capsule
15 to < 20	250	one 200 mg capsule + one 50 mg capsule
20 to < 25	300	three 100 mg capsules
25 to < 32.5	350	three 100 mg capsules + one 50 mg capsule
32.5 to < 40	400	two 200 mg capsules
≥ 40	600	one 600 mg tablet OR three 200 mg capsules

*For information on the bioavailability of the capsule contents mixed with food vehicles, see section 5.2.

Special populations

Paediatric population

The safety and efficacy of efavirenz in children below the age of 3 ~~years~~ months or weighing less than ~~13~~ 3.5 kg have not ~~yet~~ been established. ~~Currently~~ No data are available ~~data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made~~.

Method of administration

~~*Alternative method of administration*~~

Patients who cannot swallow

For ~~children~~ Capsule sprinkle: for patients at least 3 ~~years~~ months old and weighing at least ~~13 kg and adults~~ 3.5 kg who cannot ~~reliably~~ swallow ~~hard~~ capsules, ~~efavirenz oral solution is the preferred formulation. Administration of~~ the capsule contents can be administered with a small amount ~~(1-2 teaspoons) of food may be considered for patients who cannot tolerate the oral solution~~ of food using the capsule sprinkle method of administration (see section 6.6 for instructions). No additional food should be consumed for up to 2 hours after administration of efavirenz. ~~There are limited safety and tolerability data for administration of the capsule contents in paediatric patients~~.

4.4 Special warnings and precautions for use

Paediatric population

Efavirenz has not been evaluated in children below 3 ~~years~~ months of age or who weigh less than ~~13~~ 3.5 kg. Therefore, efavirenz should not be given to children less than 3 ~~years~~ months of age.

Rash was reported in ~~26 of 57~~ 59 of 182 children (~~46~~32%) treated with efavirenz ~~during a 48-week period~~ and was severe in ~~three~~ six patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

4.8 Undesirable effects

Paediatric population

Undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (~~in a clinical study including 57 children who received efavirenz during a 48-week period, rash was reported in 46%~~59 of 182 (32%) treated with efavirenz) and was more often of higher grade than in adults (severe rash was reported in ~~5.3%~~ 6 of 182 (3.3%) of children). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered. ~~Although nervous system symptoms are difficult for young children to report, they appear to be less frequent in children and were generally mild. In the study of 57 children, 3.5% of patients experienced nervous system symptoms of moderate intensity,~~

~~predominantly dizziness. No child had severe symptoms or had to discontinue because of nervous system symptoms~~.

5.1 Pharmacodynamic properties

Paediatric population

~~ACTG 382 is an ongoing uncontrolled study of 57 NRTI-experienced paediatric patients (3 - 16 years) which characterises the pharmacokinetics, antiviral activity and safety of efavirenz in combination with nelfinavir (20 - 30 mg/kg given three times a day) and one or more NRTIs. The starting dose of efavirenz was the equivalent of a 600 mg dose (adjusted from calculated body size based on weight). The response rate, based on the NC = F analysis of the percentage of patients with plasma HIV-RNA < 400 copies/ml at 48 weeks was 60% (95%, C.I. 47, 72), and 53% (C.I. 40, 66) based on percentage of patients with plasma HIV-RNA < 50 copies/ml. The mean CD4 cell counts were increased by 63 ± 34.5 cells/mm^3 from baseline. The durability of the response was similar to that seen in adult patients.~~

Study AI266922 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in antiretroviral-naive and -experienced paediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with SUSTIVA. At baseline, median plasma HIV-1 RNA was 5.88 $\log_{10}$ copies/mL, median CD4+ cell count was 1144 cells/mm^3, and median CD4+ percentage was 25%. The median time on study therapy was 132 weeks; 27% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (21/37) and 46% (17/37), respectively. The median increase from baseline in CD4+ count at 48 weeks was 215 cells/mm^3 and the median increase in CD4+ percentage was 6%.

Study PACTG 1021 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in paediatric patients who were antiretroviral therapy naive. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with SUSTIVA. At baseline, median plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL, median CD4+ cell count was 367 cells/mm^3, and median CD4+ percentage was 18%. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 77% (33/43) and 70% (30/43), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 238 cells/mm^3 and the median increase in CD4+ percentage was 13%.

Study PACTG 382 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with nelfinavir and an NRTI in antiretroviral-naive and NRTI-experienced paediatric patients. One hundred two patients 3 months to 16 years of age (median 5.7 years) were treated with SUSTIVA. Eighty-seven percent of patients had received prior antiretroviral therapy. At baseline, median plasma HIV-1 RNA was 4.57 $\log_{10}$ copies/mL, median CD4+ cell count was 755 cells/mm^3, and median CD4+ percentage was 30%. The median time on study therapy was 118 weeks; 25% of patients discontinued before

Week 48. Using an ITT analysis, the overall proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (58/102) and 43% (44/102), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 128 cells/mm^3 and the median increase in CD4+ percentage was 5%.

5.2 Pharmacokinetic properties

Paediatric population

~~In 49 paediatric patients receiving the equivalent of a 600 mg dose of efavirenz (dose adjusted from calculated body size based on weight), steady state C_{max} was 14.1 µM, steady state C_{min} was 5.6 µM, and AUC was 216 µM·h. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.~~

The pharmacokinetic parameters for efavirenz at steady state in paediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 5 by weight ranges that correspond to the recommended doses.

Table 5: Predicted steady-state pharmacokinetics of efavirenz (capsules/capsule sprinkles) in HIV-infected paediatric patients

Body Weight	Dose	Mean $AUC_{(0-24)}$ µM·h	Mean C_{max} µg/mL	Mean C_{min} µg/mL
3.5-5 kg	100 mg	220.52	5.81	2.43
5-7.5 kg	150 mg	262.62	7.07	2.71
7.5-10 kg	200 mg	284.28	7.75	2.87
10-15 kg	200 mg	238.14	6.54	2.32
15-20 kg	250 mg	233.98	6.47	2.3
20-25 kg	300 mg	257.56	7.04	2.55
25-32.5 kg	350 mg	262.37	7.12	2.68
32.5-40 kg	400 mg	259.79	6.96	2.69
>40 kg	600 mg	254.78	6.57	2.82

6.6 Special precautions for disposal and other handling

Use in the paediatric population

For ~~children~~ patients at least 3 ~~years~~ months old and weighing at least ~~13 kg and adults~~ 3.5 kg who cannot ~~reliably~~ swallow ~~hard~~ capsules, ~~efavirenz oral solution is the preferred formulation. Administration of~~ the capsule contents can be administered with a small amount (1-2 teaspoons) of food ~~may be considered for patients who cannot tolerate the oral solution. In a palatability study in healthy adults of efavirenz mixed with applesauce, grape jelly, yogurt, or infant formula, grape jelly received the highest rating of good overall taste~~using the capsule sprinkle method of administration. Patients and caregivers must be instructed to open the capsule carefully to avoid spillage or dispersion of the capsule contents into the air. It is recommended to hold the capsule ~~vertically~~ with the cap facing up and to pull the cap away from the body of the capsule, and to mix the capsule contents with food in a small container. The mixture should be administered as soon as possible, but no more than 30 minutes after mixing. After administration of the efavirenz-food mixture, an additional small amount (approximately 2 teaspoons) of food must be added to the empty mixing container, stirred to disperse any remaining residue of the medicinal product, and administered to the patient. No additional food should be consumed for up to 2 hours after administration of efavirenz.

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PACKAGE LEAFLET

2. What you need to know before you take SUSTIVA

Children and adolescents

SUSTIVA is not recommeded for children under the age of 3 ~~years~~ months or weighing less than ~~13~~ 3.5 kg because it has not been adequately studied in these patients.

3. How to take SUSTIVA

(Note: changes to this section are applicable to the PL of the capsule formulation only)

Use in children and adolescents

- SUSTIVA 50 mg hard capsules can be taken by children and adolescents 3 ~~years~~ months of age and older and weighing at least ~~13~~ 3.5 kg who are able to swallow the capsules. Opening the capsule and taking the contents with a small amount of food may be considered for children who cannot swallow the hard capsule ~~and cannot tolerate the oral solution~~.
- The dose for children ~~weighing 40 kg or more is 600 mg once daily.~~ ~~The dose for children weighing less than 40 kg~~ and adolescents is calculated by body weight and is taken once daily as shown below:

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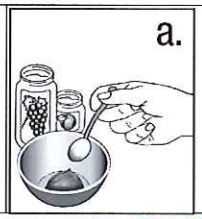
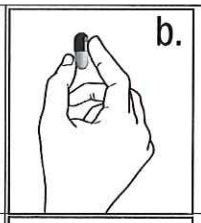
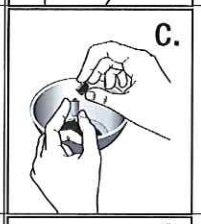
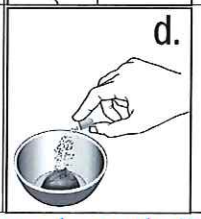
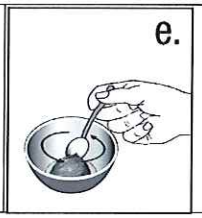
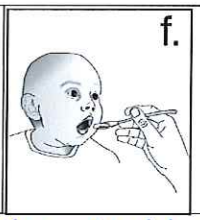
Body Weight kg	SUSTIVA Dose (mg)	Number of Capsules or Tablets and Strength to Administer
3.5 to < 5	100	one 100 mg capsule
5 to < 7.5	150	one 100 mg capsule + one 50 mg capsule
~~13~~ 7.5 to < 15	200	one 200 mg capsule
15 to < 20	250	one 200 mg capsule + one 50 mg capsule
20 to < 25	300	three 100 mg capsules
25 to < 32.5	350	three 100 mg capsules + one 50 mg capsule
32.5 to < 40	400	two 200 mg capsules
≥ 40	600	one 600 mg tablet OR three 200 mg capsules

SUSTIVA ~~oral solution is preferred for~~ For children who are not able to swallow the capsules~~. However, if a child does not tolerate the oral solution~~, the doctor may recommend opening the hard capsule and mixing the contents with a small amount (1-2 teaspoons) of food (e.g., ~~applesauce, grape jelly, yogurt or infant formula). In a taste preference study, efavirenz mixed with grape jelly received the highest rating~~yogurt). The capsules must be opened carefully so that the contents do not spill or escape into the air. Hold the capsule ~~vertically~~ with the cap facing up and pull the cap away from the body of the capsule. Use a small container for mixing. Give the mixture to the child as soon as possible, but no more than 30 minutes after mixing. Make sure the child eats the full amount of the mixture of food and capsule contents. Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container, stirring to make sure there is no ~~medicine~~ drug residue remaining in the container, and have the child eat the full amount again. The child should not be given any additional food for 2 hours. The doctor may also recommend this method of taking ~~SUSTIVA~~ Sustiva for adults who cannot swallow capsules ~~and do not tolerate the oral solution~~.

Instructions for capsule sprinkle method:

1	Avoid giving the daily SUSTIVA dose within 1 hour after a feeding or meal.
2	Wash and dry your hands before and after preparing the capsule sprinkle.
3	Choose a soft food the child likes. Examples of soft foods are applesauce, grape jelly, yogurt, or infant formula. In a taste preference study in adults, SUSTIVA mixed with grape jelly

	received the best rating.	
4	Place 1-2 teaspoons of the food in a small container (illustration a).	 a.
5	**SUSTIVA capsules must be opened carefully over the food container**, as described in steps 6-7, **so that the contents do not spill.**	
6	With your hands over the container, hold the capsule with the cap facing up (see illustration b).	 b.
7	Carefully pull the cap away from the body of the capsule (illustration c).	 c.
8	Sprinkle the contents of the capsule on the food (illustration d).	 d.
9	If the daily dose consists of more than one capsule, follow steps 5-8 for each capsule. **Do not** add more food.	
10	Mix the capsule contents and food together (illustration e).	 e.
Steps 11-14 must be completed within 30 minutes of mixing:		
11	Give the mixture of food and capsule contents to the child, making sure he or she eats the full amount (illustration f).	 f.
12	Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container (illustration a).	

13	Stir to make sure there is no drug residue remaining in the container (illustration e).
14	Have the child eat the full amount again (illustration f).
15	**Do not give the child any additional food for 2 hours.**