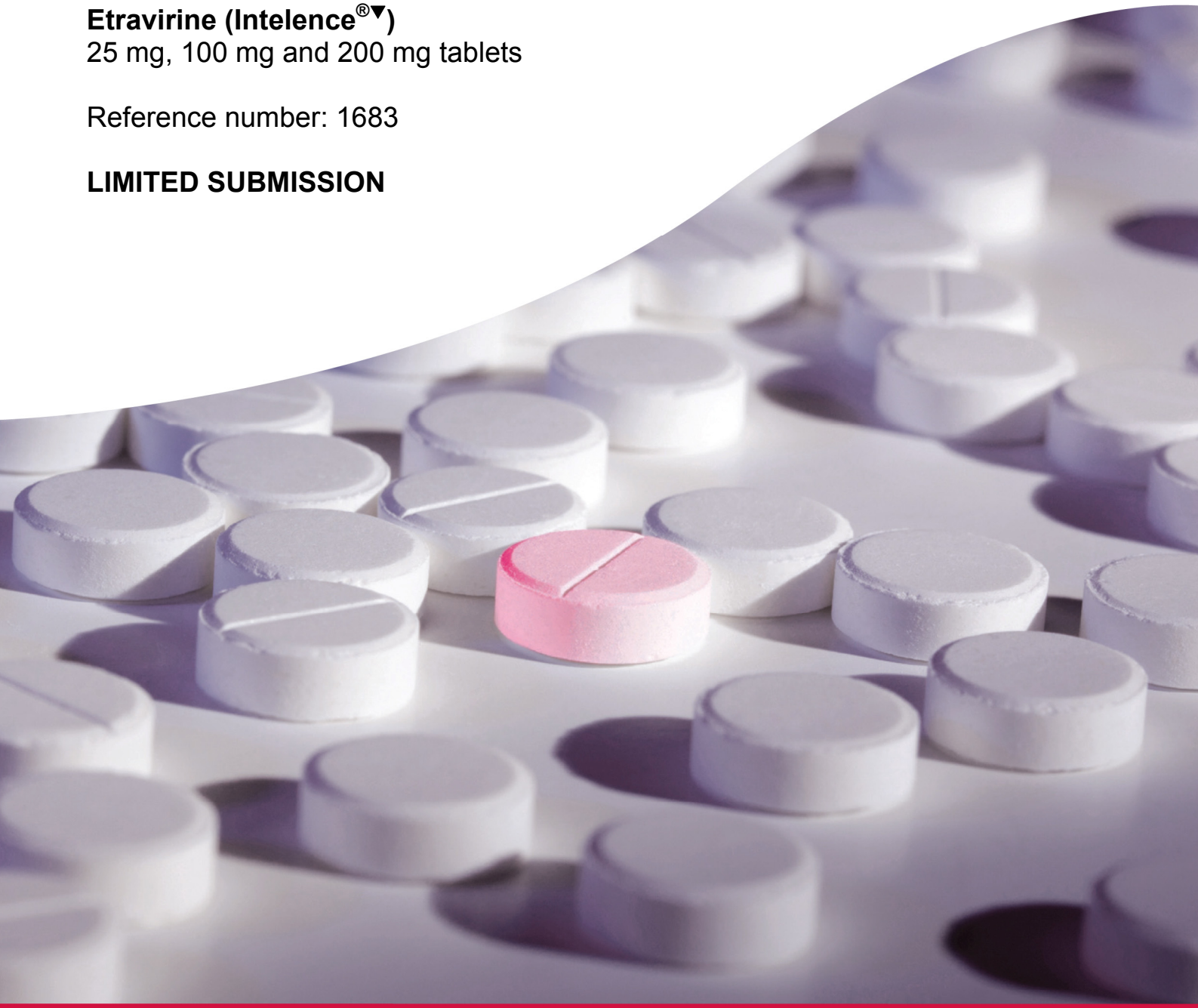
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Etravirine (Intelence®▼)
25 mg, 100 mg and 200 mg tablets

Reference number: 1683

LIMITED SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Etravirine (Intelence®▼) 25 mg, 100 mg and 200 mg tablets. Reference number: 1683. October 2013.

AWMSG Secretariat Assessment Report
Etravirine (Intelence®▼) 25 mg, 100 mg and 200 mg tablets

This assessment report is based on evidence from a limited submission by Janssen-Cilag Ltd on 16 August 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Etravirine (Intelence®▼), in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced paediatric patients from 6 years to less than 18 years of age[2–4].
Marketing authorisation date	6 March 2013[5] (licensed for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients on 28 August 2008)[2–4].
Comparators	The company submission includes evidence of the effectiveness and safety of etravirine in adult patients[1].
Limited submission details	Etravirine (Intelence®▼) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes a phase IIb open-label trial (PIANO), which evaluated the safety, tolerability, pharmacokinetics and antiviral activity of etravirine in antiretroviral treatment-experienced HIV-1 infected children and adolescents[1,6]. As supporting evidence, data is provided from the DUET studies, conducted in treatment-experienced HIV-infected adult patients as part of the initial marketing authorisation application[1,7,8].

Three additional studies evaluated the pharmacokinetics of etravirine in either healthy adult volunteers or HIV-infected, treatment-experienced, paediatric patients (6 years to less than 18 years)[1,8–10]. The pharmacokinetics of equivalent doses of the 25 mg and 200 mg tablets were concluded to be comparable to the 100 mg tablet[9,10]. Additionally, the Committee for Medicinal Products for Human Use (CHMP) considered the pharmacokinetics of etravirine in paediatric patients and concluded that the administered weight-based dosages resulted in etravirine exposure comparable to that in adults receiving etravirine 200 mg twice daily when administered at a dose corresponding to 5.2 mg/kg twice daily[1,8].

2.1 PIANO study

This phase IIb, open-label, 48-week study assessed the safety, tolerability, pharmacokinetics and antiviral activity of etravirine plus optimised background regimen in treatment-experienced HIV-1 infected paediatric patients (aged 6 years to less than 18 years)[1,6,8]. Patients (n = 101; 41 aged 6 years to less than 12 years and 60 aged 12 years to less than 18 years) received etravirine administered with food at a dose of 5.2 mg/kg (maximum dose: 200 mg) twice daily[8].

Patients also received an investigator-selected optimised background regimen consisting of at least two antiretroviral medicines, comprising a boosted protease inhibitor plus a nucleoside reverse transcriptase inhibitor (NRTI); use of enfuvirtide (Fuzeon®) and/or raltegravir (Isentress®) was optional. Eligible patients had a body weight ≥ 16 kg and HIV-1 plasma viral load ≥ 500 copies/ml at screening[8].

The primary objective was to evaluate the safety and tolerability of etravirine in combination with other antiretroviral therapies over a 24-week treatment period in children and adolescents aged 6 to < 18 years. The primary efficacy endpoint was the percentage of subjects with plasma viral load < 50 copies/ml at week 24. Additional secondary objectives included further analysis of the antiviral activity of etravirine and evaluation of the immunological changes[8]. The study also evaluated the safety profile and pharmacokinetic parameters over the 48-week treatment period.

At week 24, 53/101 (52.5%) patients had virologic response, defined as plasma viral load < 50 copies/ml (24/41 [58.5%] in children aged ≥ 6 to < 12 years; 29/60 [48.3%] in adolescents aged ≥ 12 to < 18 years). At week 48, the proportion of responders with viral load < 50 copies/ml was 56.4%, suggesting that virologic suppression was sustained. This was supported by analysis of other measures of antiviral activity and immunological outcomes (see Table 1)[8].

At the time of licensing, CHMP noted that the virologic suppression achieved during the PIANO study was similar to that observed in adults during the DUET studies (conducted in adult HIV-infected patients as part of the initial marketing authorisation application), while the collected safety data did not give rise to new safety concerns in the paediatric population[8].

Table 1. Comparison of the PIANO and DUET study outcomes.

	PIANO study			Pooled DUET etravirine treatment arms
	All patients	**6 to < 12 years**	**12 to < 18 years**	
n	101	41	60	599
Virologic parameters				
Patients with viral load < 50 copies/ml at week 24	52 (51.5%)	24 (58.5%)	28 (46.7%)	363 (60.6%)
Patients with viral load < 400 copies/ml at week 24	66 (65.3%)	28 (68.3%)	38 (63.3%)	445 (74.3%)
Patients with ≥ 1 $\log_{10}$ decrease from baseline at week 24	64 (63.4%)	26 (63.4%)	38 (63.3%)	475 (79.3%)
Mean change from baseline in $\log_{10}$ viral load (copies/ml) at week 24 (Standard error)	−1.51 (0.16)	−1.62 (0.21)	−1.44 (0.17)	−2.37 (0.05)
Median change from baseline in $\log_{10}$ viral load (copies/ml) at week 24 (Range)	−1.68 (−4.3; 0.9)	−1.68 (−4.3; 0.9)	−1.68 (−4.0; 0.7)	−2.78 (−4.6; 1.4)
Immunologic parameters				
Mean change from baseline in CD4 cell count (x 10^6 cells/l) (Standard error)	112 (16.9)	125 (33.0)	104 (17.5)	83.5 (3.64)
Median change from baseline in CD4 cell count (x 10^6 cells/l) (Range)	108 (−410; 718)	124 (−410; 718)	81 (−243; 472)	77.5 (−331; 517)
Median change from baseline in CD4 percentage (Range)	4% (−9; 20)	4% (−9; 20)	3% (−4; 14)	3% (−7; 23)

During the PIANO study, 33/101 (32.7%) patients reported an adverse event (AE) at least possibly related to etravirine treatment, while 16/101 (15.8%) patients reported serious AEs (regardless of causality)[6]. No fatalities were reported but eight (7.9%) patients discontinued due to an AE. The most commonly reported AEs were upper respiratory tract infection (26.7%), rash (22.8%), diarrhoea (15.8%), cough (11.9%), nausea (9.9%) and vomiting (9.9%)[6].

2.2 Points to note

- The company submission includes a comparison between etravirine in paediatric patients and use in adult patients[1]. In its guideline on the clinical development of medicinal products for the treatment of HIV infection, CHMP stipulates that extrapolation to children from efficacy data obtained in adults is acceptable if reliable pharmacokinetic data allow for proper dose recommendations[11]. Given the similarity of the disease in adults and children, CHMP acknowledged that there is no need to duplicate the evidence of efficacy obtained in adults, since the dose has been adequately selected on the basis of the adult exposure[8].
- At the time of licensing, CHMP considered the pharmacokinetic, efficacy and safety data obtained for etravirine use in children, and concluded that they were similar to those obtained in adults[8].
- AWMSG recommended etravirine (Intelence®) in 2009 as an option for use within NHS Wales for the treatment of HIV-1 infected, antiretroviral treatment-experienced adults in combination with a boosted protease inhibitor and other antiretroviral medicinal products[12].
- The 2009 Paediatric European Network for the Treatment of AIDS (PENTA) guidelines state that the preferred first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) is nevirapine (Viramune®) for children aged < 3 years, and efavirenz (Sustiva®) for older children[13]. However, the applicant company notes that etravirine is indicated for treatment-experienced paediatric patients from 6 years of age and suggests that etravirine does not therefore have the same place in therapy as nevirapine or efavirenz[1]. Furthermore, the applicant company states that it is not feasible to provide a comparison between etravirine and nevirapine or efavirenz, as there is no direct comparative evidence in this patient population and there is no common comparator arm in the trials with which to facilitate an indirect comparison.
- During the PIANO study, 93% of adolescents received the adult etravirine dose (200 mg twice daily)[8]. However, the exposure in this age group was lower than observed in adults. In addition, fewer adolescents than children achieved a virologic response, defined as plasma viral load < 50 copies/ml, at 24 and 48 weeks. Poorer adherence in adolescents could have driven this finding, but this relationship could not be established due to limitations in the adherence data collected. However, CHMP noted that in observant patients (adherence > 95% assessed by pill count), measures of bioavailability remained higher in children than adolescents[8].
- Etravirine is administered twice daily[2–4], while efavirenz and prolonged-release nevirapine are both taken once daily[14–19], which could impact patient preference. Additionally, the safety and efficacy of etravirine in children less than 6 years of age or weighing less than 16 kg have not yet been established[2–4], while efavirenz can be used in children aged three years and over and weighing at least 13 kg[14–16] and nevirapine can be used in children of any age[17–21].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The applicant company estimates that there are 1–2 patients in Wales aged 6–18 years and eligible to receive etravirine (i.e. treatment-experienced)[1], based on prevalence data and the number of patients switching to second-line treatments in the Collaborative HIV Paediatric Study (CHIPS) cohort[22].

Additionally, it is assumed that the patient pool will remain constant over time, due to a relatively low HIV incidence rate in Wales (0.005%)[1] based on data from the Health Protection Agency[23].

According to the company submission, etravirine would cost £1,833–£3,666 per patient per year (depending upon patient weight)[1]. Therefore, the estimated annual cost of treating two patients with etravirine will range from £3,665 to £7,331, and the five-year budget impact will range from £18,327 to £36,655, depending on the weight of the patients.

3.2 AWTTC critique of the budget impact analysis

- The company submission assumes that all eligible patients switch to etravirine[1]. However, this does not take into account use of nevirapine and efavirenz and so may not reflect use of etravirine in NHS Wales.
- The number of treatment-experienced patients eligible for etravirine therapy is based on data from the CHIPS study, where 1,791 children were enrolled, and a subset of 300 children were studied following a switch to second-line therapy after ≥ 12 months receiving first-line therapy[22]. The applicant company has assumed from this that 17% of paediatric patients could be expected to be treatment-experienced[1]. However, the CHIPS study does not specify that this subset of 300 children comprised the total number of patients that were treatment-experienced[22]. Therefore, the number of children who will be potentially eligible for treatment with etravirine is subject to a degree of uncertainty.

3.3 Comparative unit costs

Table 2 provides comparative annual acquisition costs for the maximum and minimum possible doses of NNRTI therapies, for patients aged six years and over with a minimum weight of 16 kg.

Table 2. Example comparative annual acquisition costs for NNRTI therapies in treatment-experienced HIV-1 infected paediatric patients.

Treatment	Minimum and maximum daily dose	Annual cost of treatment
Etravirine (Intelence®▼) 25 mg, 100 mg, 200 mg tablets	≥ 16 kg to < 20 kg: 100 mg twice daily ≥ 30 kg: 200 mg twice daily	£1,833 £3,665
Efavirenz (Sustiva®) 50 mg, 100 mg, 200 mg hard capsules	≥ 15 kg to < 20 kg: 250 mg once daily ≥ 40 kg: 600 mg once daily	£1,016 £2,437
Efavirenz (Sustiva®) 30 mg/ml oral solution	≥ 15 kg to < 20 kg: 10 ml once daily ≥ 40 kg: 24 ml once daily	£1,092 £2,620
Efavirenz (Sustiva®) 600 mg film-coated tablets	≥ 40 kg: 600 mg once daily	£2,437
Nevirapine (Viramune®) 200 mg tablets*	≥ 16 years or weight > 50 kg or body surface area > 1.25 m^2: 200 mg twice daily	£2,068
Nevirapine (Viramune®) 50 mg/5 ml oral suspension*	≥ 8 years of age and ≥ 15.63–21.88 kg: 7.5 ml twice daily ≥ 16 years or ≥ 8 years and > 46.88 kg or < 8 years and > 26.79 kg: 20 ml twice daily	£1,150 £3,066
Nevirapine (Viramune®) 50 mg, 100 mg, 400 mg prolonged-release tablets*	< 8 years and 12.5–17.8 kg or ≥ 8 years and 17.9–31.2 kg: 200 mg once daily < 8 years and ≥ 25 kg or ≥ 8 years and ≥ 43.8 kg: 400 mg once daily	£1,034 £2,068

* Maintenance doses only
Doses used reflect the minimum and maximum possible doses in the licensed populations, based on dosing instructions in the relevant Summaries of Product Characteristics (SPCs); refer to the SPCs for full dosing details[2–4,14–21].
Costs are based on MIMS list prices as of 27 August 2013[24].
This table does not imply therapeutic equivalence of medicines or the stated doses.

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, etravirine (Intelence®▼) is appropriate for specialist-only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that etravirine (Intelence®▼) will be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 25 and 26 July 2013.
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Janssen-Cilag Ltd. Form C: Limited appraisal submission. Etravirine (Intelence®▼). Aug 2013.

2 Janssen-Cilag Ltd. Intelence®▼ 100 mg tablets. Summary of Product Characteristics. Jun 2013. Available at: http://www.medicines.org.uk/emc/medicine/21185/SPC/Intelence+100+mg+tablets/. Accessed Aug 2013.

3 Janssen-Cilag Ltd. Intelence®▼ 200 mg tablets. Summary of Product Characteristics. Jun 2013. Available at: http://www.medicines.org.uk/emc/medicine/25606/SPC/Intelence+200mg/. Accessed Aug 2013.

4 Janssen-Cilag Ltd. Intelence®▼ 25mg tablets. Summary of Product Characteristics. Jun 2013. Available at: http://www.medicines.org.uk/emc/medicine/27659/SPC/Intelence+25mg+tablets/. Accessed Aug 2013.

5 European Medicines Agency. Intelence®. Procedural steps taken and scientific information after the authorisation. Jul 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000900/WC500034184.pdf. Accessed Aug 2013.

6 Tudor-Williams G, Cahn P, Chokephaibulkit K et al. Abstract no. TULBPE027. Safety and efficacy of etravirine in HIV-1-infected, treatment-experienced children and adolescents (6-17 years): week 24 primary analysis of the phase II PIANO study. Presented at 6th IAS Conference on HIV Pathogenesis and Treatment. 2011.

7 Katlama C, Haubrich R, Lalezari J et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS* 2009; 23 (17): 2289-300.

8 European Medicines Agency. CHMP assessment report: Intelence®. Procedure No.: EMEA/H/C/000900/X/0018/G. Apr 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000900/WC500141972.pdf. Accessed Aug 2013.

9 Schöller-Gyüre M, Kakuda TN, Van Solingen-Ristea RM et al. Abstract no. MOPE0184. Bioavailability of the 100mg etravirine tablet dispersed in water and of the 25mg pediatric tablet formulation. Presented at AIDS 2008 - XVII International AIDS Conference. 2008.

10 Kakuda T, de Smedt G, Leemans R et al. Abstract no. MOPE175. Bioavailability of etravirine 200mg administered as a single 200-mg tablet versus two 100-mg tablets in HIV-negative, healthy volunteers. Presented at 6th IAS Conference on HIV Pathogenesis and Treatment. 2011.

11 European Medicines Agency. CPMP/EWP/633/02. Guideline on the clinical development of medicinal products for the treatment of HIV infection. Nov 2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003460.pdf. Accessed Aug 2013.

12 All Wales Medicines Strategy Group. Etravirine (Intelence®). Reference No. 140. Sep 2009. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/140. Accessed Aug 2013.

13 Welch S, Sharland M, Lyall EG et al. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Med* 2009; 10 (10): 591-613. Available at: http://www.pentatrials.org/HIV_759.pdf.

14 Bristol-Myers Squibb Pharmaceutical Ltd. Sustiva® 30 mg/ml oral solution. Summary of Product Characteristics. Jun 2013. Available at: http://www.medicines.org.uk/emc/medicine/10381/SPC/Sustiva+30+mg+ml+Oral+Solution/. Accessed Aug 2013.

15 Bristol-Myers Squibb Pharmaceutical Ltd. Sustiva® 50 mg, 100 mg and 200 mg hard capsules. Summary of Product Characteristics. Jun 2013. Available at: http://www.medicines.org.uk/emc/medicine/9877/SPC/Sustiva+50+mg%2c+100+mg+and++200+mg++Hard+Capsules/. Accessed Aug 2013.
16 Bristol-Myers Squibb Pharmaceutical Ltd. Sustiva® 600 mg film-coated tablets. Summary of Product Characteristics. Jun 2013. Available at: http://www.medicines.org.uk/emc/medicine/11284/SPC/Sustiva+600+mg+Film-Coated+Tablets/. Accessed Aug 2013.
17 Boehringer Ingelheim Ltd. Viramune® 100 mg prolonged-release tablets. Summary of Product Characteristics. Jul 2013. Available at: http://www.medicines.org.uk/emc/medicine/25116/SPC/Viramune+100+mg+Prolonged-Release+Tablets/. Accessed Aug 2013.
18 Boehringer Ingelheim Ltd. Viramune® 50 mg prolonged-release tablets. Summary of Product Characteristics. Jul 2013. Available at: http://www.medicines.org.uk/emc/medicine/25115/SPC/Viramune+50+mg+Prolonged-Release+Tablets/. Accessed Aug 2013.
19 Boehringer Ingelheim Ltd. Viramune® 400 mg prolonged-release tablets. Summary of Product Characteristics. Jul 2013. Available at: http://www.medicines.org.uk/emc/medicine/25117/SPC/Viramune+400+mg+Prolonged-Release+Tablets/. Accessed Aug 2013.
20 Boehringer Ingelheim Ltd. Viramune® 200 mg tablets. Summary of Product Characteristics. May 2013. Available at: http://www.medicines.org.uk/emc/medicine/322/SPC/Viramune+200mg+Tablets/. Accessed Aug 2013.
21 Boehringer Ingelheim Ltd. Viramune® 50 mg/5 ml oral suspension. Summary of Product Characteristics. May 2013. Available at: http://www.medicines.org.uk/emc/medicine/2343/SPC/Viramune+50mg+5ml+oral+Suspension/. Accessed Aug 2013.
22 Collaborative HIV Paediatric Study. Data from the Collaborative HIV Paediatric Study (CHIPS): reports up to March 2012. 2012.
23 Public Health England, Health Protection Scotland, UCL Institute of Child Health. United Kingdom: new HIV diagnoses to end of December 2012. 2013. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_c/1237970242135. Accessed Aug 2013.
24 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2013. Available at: http://www.mims.co.uk/.