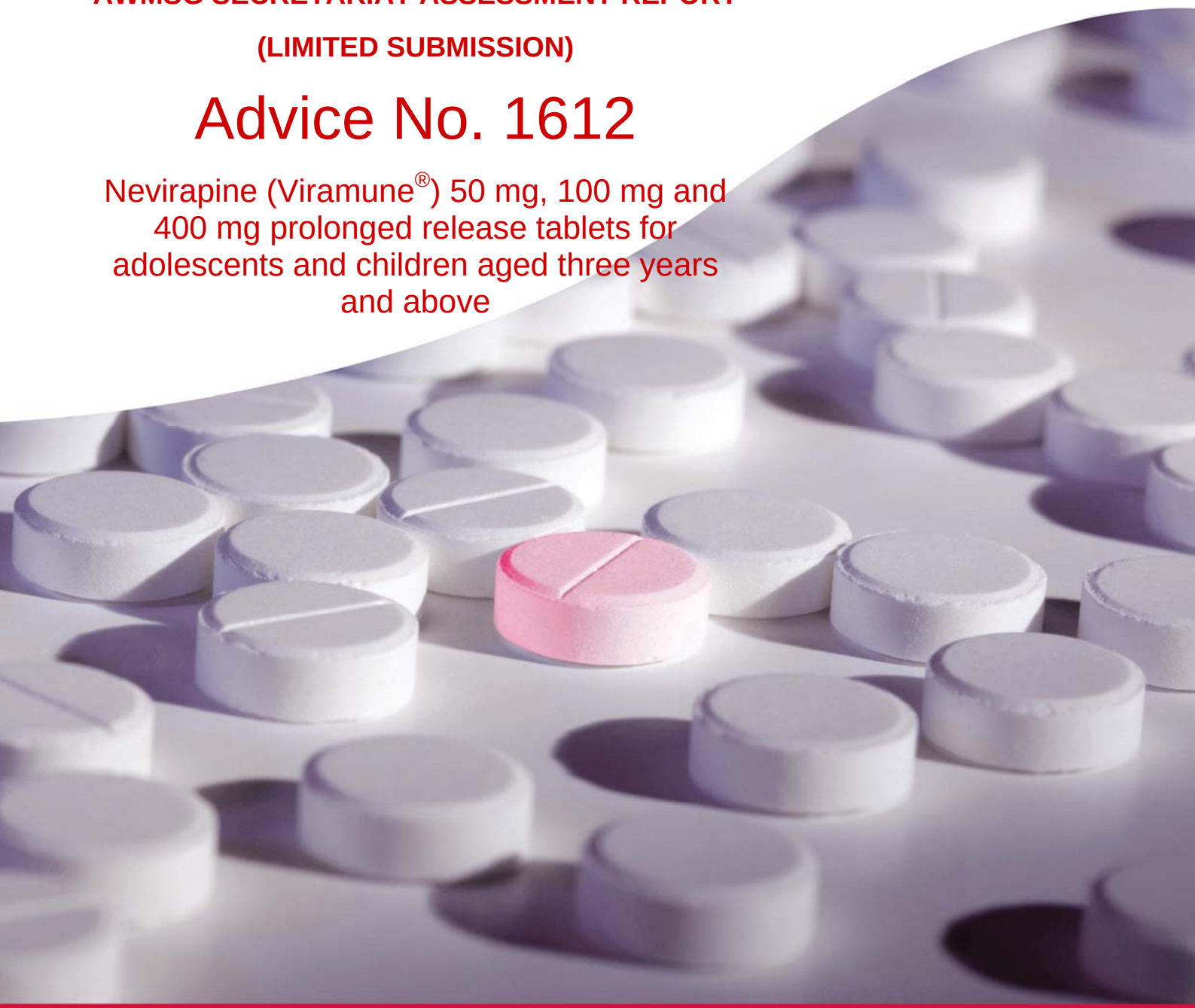
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 1612

Nevirapine (Viramune®) 50 mg, 100 mg and 400 mg prolonged release tablets for adolescents and children aged three years and above



AWMSG Secretariat Assessment Report – Advice No. 1612
Nevirapine (Viramune®) 50 mg, 100 mg and 400 mg prolonged release tablets for adolescents and children aged three years and above

This assessment report is based on evidence from a limited submission by Boehringer Ingelheim Ltd on 17 January 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Nevirapine 50 mg, 100 mg and 400 mg prolonged release (PR) tablets are indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infected adolescents and children three years and above and able to swallow tablets[2–4]. Nevirapine 400 mg PR tablets are also licensed for the treatment of HIV-1 infected adults. The All Wales Medicines Strategy Group (AWMSG) is considering the use of nevirapine 400 mg PR in adults as part of a separate appraisal[5]. PR tablets are not suitable for the 14-day lead-in phase for patients starting nevirapine. Other nevirapine formulations, such as immediate release (IR) tablets or oral suspension should be used[2–4]. Most of the experience with Viramune® is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). The choice of a subsequent therapy after Viramune® should be based on clinical experience and resistance testing[2–4].
Dosing	Nevirapine 50 mg and 100 mg PR tablets are dosed based on the patient's weight or body surface area (see Summary of Product Characteristics [SPC] for dosing calculations). Lead-in dosing is with nevirapine 200 mg IR tablets or 50 mg/5 ml oral suspension for the first 14 days[2,3]. The recommended regimen for patients initiating nevirapine 400 mg PR therapy is one 200 mg IR tablet daily for the first 14 days, followed by one 400 mg PR tablet daily. Nevirapine 400 mg PR tablets can be taken by children, following the adult dosing schedule, if they: • are ≥ 8 years of age and weigh 43.8 kg or more or • are < 8 years of age and weigh 25 kg or more or • have a body surface area of 1.17 m^2 or above according to the Mosteller formula[4]. The lead-in period is not required if the patient is already receiving a regimen of nevirapine 200 mg IR tablets or 50 mg/5 ml oral suspension twice-daily. Nevirapine should be combined with at least two additional antiretroviral agents[2–4].
Marketing authorisation date	16 September 2011[6].

2.0 DECISION CONTEXT

2.1 Background

According to Health Protection Agency data, as of June 2011, 88 patients ≤ 19 years of age have been diagnosed with HIV in Wales, with an average of five new cases diagnosed each year between 2000 and 2011 in this age bracket[7]. HIV leads to a reduction in $CD4^+$ lymphocytes of the infected host[8]. Clinical guidelines recommend referring to the patient's $CD4^+$ count to decide when to begin antiretroviral treatment during HIV infection[9,10]. The choice of regimen for paediatric HIV-1 infection should be guided by patient age, abacavir (Ziagen®) sensitivity and other factors such as the ability of the patient to adhere to and tolerate individual drugs[9]. An antiretroviral regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) is recommended first-line in newly diagnosed HIV-1 paediatric patients in whom treatment is deemed appropriate[9,10].

NNRTIs can be associated with safety and tolerability problems (mainly hepatotoxicity, central nervous system symptoms, and/or rash)[11]. Poor adherence to antiretroviral therapy has been shown to increase the risk of incomplete viral suppression, disease progression and death[12]. Nevirapine is an NNRTI which exhibits non-competitive inhibition of the reverse transcriptase of HIV-1, but does not have a biologically significant inhibitory effect on the HIV-2 reverse transcriptase or on eukaryotic DNA polymerases α, β, γ or δ[4]. Nevirapine has historically been used twice-daily as 200 mg IR tablets. It has been proposed that the use of once-daily dosing with PR tablets will increase patient convenience and therefore compliance[13,14]. As nevirapine causes induction of its own metabolism, a 14-day lead-in period with nevirapine 200 mg IR tablets or 50 mg/5 ml oral suspension, administered once-daily, is required[2–4,15]. This lead-in period has been found to lessen the frequency of rash in patients treated with nevirapine[2–4].

2.2 Comparators

The comparators requested by the Welsh Medicines Partnership (WMP)[*] were nevirapine 200 mg IR tablets twice-daily and 50 mg/5 ml oral suspension.

2.3 Guidance and related advice

- Paediatric European Network for Treatment of AIDS (PENTA) guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection (2009)[9].
- World Health Organization (WHO). Antiretroviral therapy of HIV infection in infants and children: Towards universal access. Recommendations for a public health approach (2006)[10].

AWMSG is concurrently considering:

- Nevirapine (Viramune®) 400 mg PR tablets in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults[5].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included results from two randomised trials (VERxVE and TRANxITION) in which the non-inferiority of nevirapine once-daily 400 mg PR tablets, compared with nevirapine twice-daily 200 mg IR tablets, in adults was

[*] In April 2012 the Welsh Medicines Partnership became part of the All Wales Therapeutics and Toxicology Centre (AWTTC)

demonstrated[1,13,14]. These studies were conducted in patients aged ≥ 18 years and are discussed in detail in the AWMSG Secretariat Assessment Report for nevirapine 400 mg PR tablets for adult use[5]. In support of the use of nevirapine 100 mg and 400mg PR tablets in adolescents and children, the company provided results from an open-label, cross-over, steady-state pharmacokinetics (PK) trial (study 1100.1518)[1,16]. To support the use of the 50 mg and 100 mg PR tablets, two open-label, single dose, parallel-group phase I PK studies (randomised study 1100.1531 and non-randomised study 1100.1517) were provided. These studies were conducted in healthy, adult (≥ 18 years) male volunteers[17,18]. The more relevant trials for each formulation are discussed below.

3.1 Paediatric pharmacokinetics

Eighty-five patients aged ≥ 3 to ≤ 18 years with viral load of < 50 RNA copies/ml that had previously received treatment with a nevirapine IR regimen for at least 18 weeks entered study 1100.1518. Of these, 71/85 (83.5%) had received a nevirapine-based regimen for two or more years. Patients were stratified by age and entered into a lead-in phase in which they received ten days of nevirapine IR (dose calculated by same methods applied prior to study enrolment). Patients were then switched to nevirapine PR at doses of 200 mg (two 100 mg tablets), 300 mg (three 100 mg tablets) or 400 mg (one 400 mg tablet) for ten days, based on nevirapine IR dose previously received. Results indicated that the nevirapine PR profile is more constant than the IR profile, suggesting nevirapine was slowly released and absorbed from PR tablets[1,19]. The target C_{min} was achieved with the nevirapine PR formulation[19].

The comparative bioavailability of the nevirapine 50 mg PR tablet was determined in an open-label, randomised, single dose, parallel-group phase I PK trial (study 1100.1531) which compared nevirapine 200 mg PR as two 100 mg PR tablets with four 50 mg PR tablets in healthy male volunteers (n = 48). The relative bioavailability of the 50 mg tablet compared with the 100 mg tablet was 106.7% (90% CI: 92.8% to 122.7%) for C_{max} and 111.1% (90% CI: 93.0% to 132.8%) for $AUC_{0-\infty}$[17,19]. Nevirapine exposure was concluded to be higher in patients receiving the four 50 mg tablets, and these could not be regarded as bioequivalent to the two 100 mg tablets[17,19] (see Section 3.3).

3.2 Comparative safety

The safety profile of nevirapine, including rash and severe or life-threatening incidences of skin reaction, hepatoxicity and granulocytopenia, is documented[2–4]. The active ingredient used in nevirapine PR tablets is identical to that used in nevirapine 200 mg IR tablets, therefore the Committee for Medicinal Products for Human Use (CHMP) expected that the safety profile would be comparable[19]. The comparative safety of nevirapine 400 mg PR tablets and nevirapine 200 mg IR tablets in adult HIV-1 patients, as presented in the VERxVE and TRANxITION studies, is discussed in the AWMSG Secretariat Assessment Report for nevirapine 400 mg PR tablets for adult use[5].

During study 1100.1518, adverse events (AEs) were reported in 24/85 (28.2%) patients during the nevirapine 200 mg IR lead-in phase and in 39/83 (46.9%) patients during the nevirapine PR phase. AWTTC note that there was a higher number of infections and infestations in the PR phase[19]. Treatment-related headache was reported in four patients during the IR phase and one patient in the PR phase. No AEs leading to discontinuation were observed[16].

In study 1100.1531 there was no difference in the frequency of healthy male volunteers who experienced AEs (10/24 [41.7%] in each group). Headache was the most frequently reported AE and was higher in subjects treated with four 50 mg nevirapine

PR tablets (5/24 [20.8%; two incidents were considered treatment-related], one severe) than in subjects treated with two 100 mg nevirapine PR tablets (2/24 [8.3%])[17].

3.3 AWTTC critique

- CHMP accept that the efficacy of nevirapine PR is non-inferior to that of nevirapine IR in both treatment-naive and treatment-experienced HIV-1 infected patients. Further, CHMP conclude that in children taking the PR formulation, the nevirapine exposure is similar to that observed in adult treatment-naive patients in the 48-week study[19].
- CHMP conclude that no new safety signals were observed with the use of nevirapine PR[19].
- CHMP concluded that comparable bioavailability, exposure and viral suppression was demonstrated between the IR and PR formulations in paediatric patients based on a short-term, phase I switch study conducted in 85 children aged ≥ 3 to ≤ 18 years (see efficacy data in Section 3.1)[19]. The 400 mg and 100 mg PR tablets and the IR formulations are therefore considered interchangeable.
- Although criteria for bioequivalence was not fulfilled during study 1100.1531, CHMP concluded that the higher exposure observed with the nevirapine 50 mg PR tablets compensates for the lower bioavailability observed with the two nevirapine 100 mg PR tablets compared with nevirapine 200 mg IR[19]. The SPC for the 50 mg PR tablets states that "dividing a 200 mg total dose into four 50 mg doses rather than two 100 mg doses produced a 7–11% greater overall absorption, but with comparable medicinal product release rates. The observed pharmacokinetic difference between the 50 mg and 100 mg PR tablets is not clinically relevant, and the 50 mg PR tablet can be used as an alternative to the slightly larger 100 mg tablet"[2].
- The bioavailability of the nevirapine 50 mg PR tablets has only been evaluated in healthy male adult volunteers[17,19], rather than the paediatric population under consideration in this appraisal.
- Nevirapine PR tablets have been developed with the aim of increasing patient convenience and therefore adherence. In study 1100.1518, compliance was shown to be comparable between the use of nevirapine PR and nevirapine IR[13,16]. Pill counts have, however, not been considered as robust for some time[16,20], with clinical guidelines published in 2012 still stating that pill counts performed by staff or patients are not routinely recommended as a measure of adherence[21].
- In relation to paediatric use, nevirapine PR 50 mg, 100 mg and 400 mg tablets are licensed for the treatment of adolescents and children three years and above[2–4], whereas nevirapine IR 200 mg tablets and 50 mg/5 ml oral suspension are licensed for the treatment of adolescents and children of any age[22,23].
- Of the 85 patients enrolled to the paediatric PK study, 60 were from Botswana, 12 were from Germany, 11 were from South Africa and 2 were from the USA; this may not be representative of the patient population in Wales.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

Applicant companies are not required to submit evidence on cost-effectiveness for a limited submission, and literature searches by AWTTC identified no relevant studies.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company submission contains a simple estimation of the maximum annual cost per patient of once-daily nevirapine PR tablets[1]. Since nevirapine PR tablets will be priced at parity per mg with twice-daily nevirapine IR tablets, the company suggests that there will be no budgetary impact associated with the introduction of nevirapine PR tablets in Wales.

5.1.2 AWTTC critique of the company's budget impact estimates

- The company highlighted controlled trials demonstrating non-inferiority of the PR and IR formulation tablets in adults in terms of viral response[1]. CHMP concluded that comparable bioavailability, exposure and viral suppression was demonstrated between the IR and PR formulations in paediatric patients based on a short-term, phase I switch study conducted in 85 children aged ≥ 3 to ≤ 18 years (see efficacy data in Section 3.1)[19]. The 400 mg and 100 mg PR tablets and the IR formulations are considered interchangeable (see Section 3.3).
- The IR tablet formulation of nevirapine is available only in the 200 mg strength; children unable to take the IR tablet formulation due to dosing requirements would instead use nevirapine oral suspension[23], which is more costly on a per mg basis[24]. No information is provided around the number of patients currently receiving nevirapine IR tablets or suspension in Wales, nor the anticipated market uptake for nevirapine PR tablets.
- The PR tablet formulation is available in 100 mg and 50 mg once-daily formulations for children aged three years and above who are able to swallow tablets. The extended dose range of PR formulations, compared with IR formulation, may therefore have the potential to reduce the overall use of the oral suspension in children who are able to take tablets, but who cannot take the IR tablet formulation due to dose requirements.
- The PR formulations are not suitable for the initial reduced-dose 14-day lead-in period, which still requires the use of an IR formulation[2].
- On the assumption of equivalence between IR and PR formulations, it is anticipated there will be no additional costs from the use of the PR formulation instead of the currently available IR formulations under the current pricing structure.

5.2 Comparative unit costs

Nevirapine should be used in combination with other antiretroviral agents, and HIV drug regimens are individually tailored to patients, making estimation of comparative unit costs for nevirapine and other antiretroviral agents difficult. Table 1 therefore lists the ongoing acquisition costs of the different formulations of nevirapine following the 14-day lead-in period with reduced-dose IR preparations.

Table 1. Examples of drug acquisition costs for nevirapine formulations in the treatment of HIV-1 infected adults, adolescents and children.

Drug	Regimen	Cost per patient per year
Viramune® (nevirapine) 50 mg, 100 mg and 400 mg PR tablets	200–400 mg once-daily, depending on age, body weight and/or body surface area	£1,034–2,068
Viramune® (nevirapine) 200 mg IR tablets	200 mg twice-daily	£2,068
Viramune® (nevirapine) 50 mg/5 ml oral suspension	2.5–20 ml twice-daily depending on age, body weight and/or body surface area	£383–3,066
Costs are based on MIMS list prices[24]. *See relevant Summaries of Product Characteristics for full dosing details[2,22,23].* *This table does not imply therapeutic equivalence of drugs or the stated doses.*		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that nevirapine is suitable for specialist only prescribing within NHS Wales for the above indication.

6.2 AWMSG review

This ASAR will be considered for review three years from Ministerial ratification (date will be disclosed on the Final Appraisal Recommendation).

6.3 Evidence search

Date of evidence search: 19 January 2012.
Date range of evidence search: No date limits were applied to database searches.

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