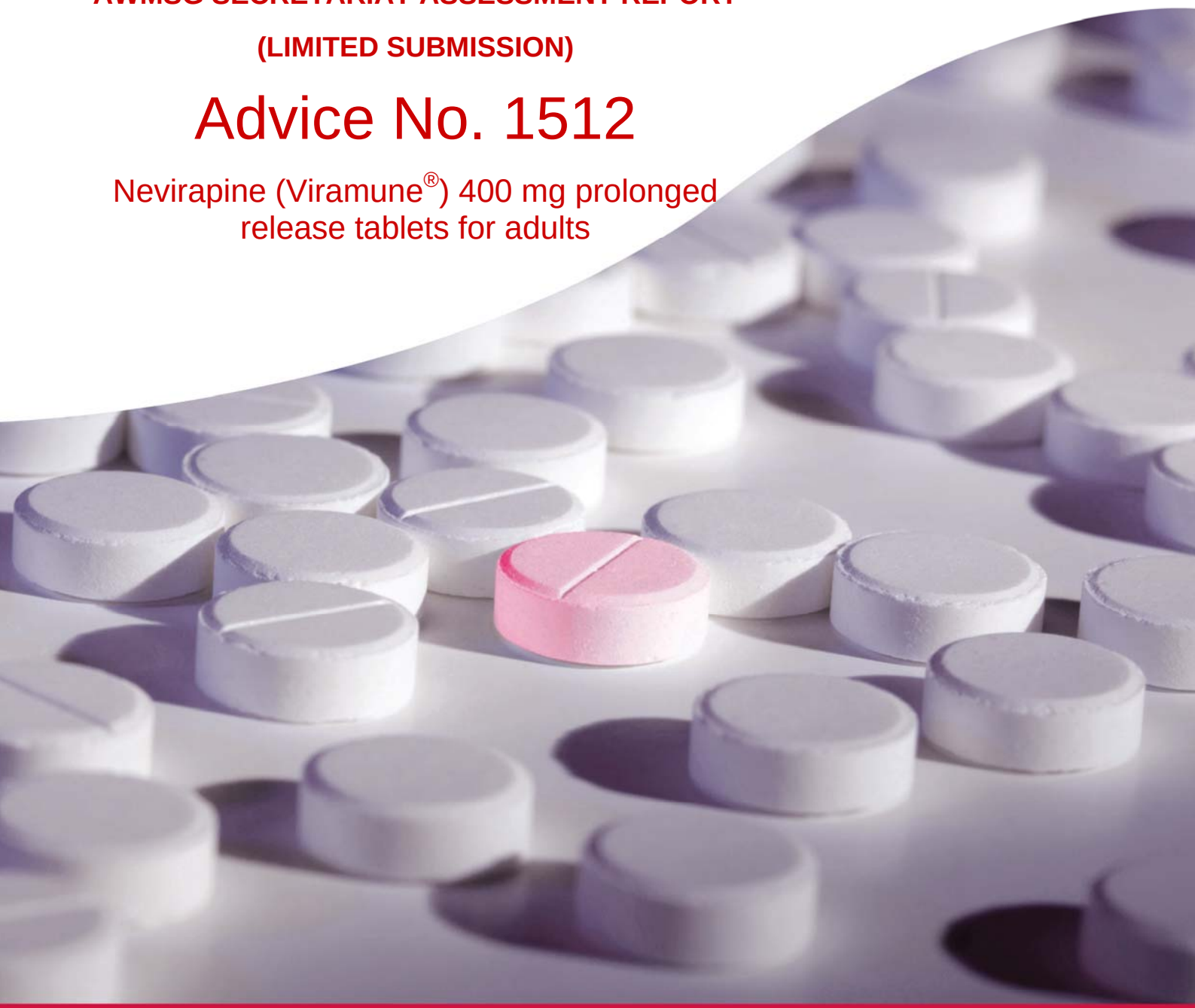
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 1512

Nevirapine (Viramune®) 400 mg prolonged release tablets for adults



AWMSG Secretariat Assessment Report – Advice No. 1512
Nevirapine (Viramune®) 400 mg prolonged release tablets for adults

This assessment report is based on evidence from a limited submission by Boehringer Ingelheim Ltd on 8 December 2011[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Nevirapine (Viramune®) 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 adults, adolescents and children three years and above and able to swallow tablets[2]. For this appraisal, the All Wales Medicines Strategy Group (AWMSG) will only consider the use of 400 mg PR tablets in adults. AWMSG is considering the use of 400 mg PR tablets in adolescents and children three years and above and able to swallow tablets as part of a separate appraisal[3]. 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]. 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].
Dosing	The recommended dose for adult patients initiating nevirapine therapy is one 200 mg IR tablet daily for the first 14 days (lead-in period), followed by one 400 mg PR tablet daily, in combination with at least two additional antiretroviral agents. Adult patients already on a regimen of nevirapine IR twice daily in combination with other antiretroviral agents can be switched to 400 mg PR tablets once-daily in combination with other antiretroviral agents without a lead-in period. Nevirapine 400 mg PR has not been specifically investigated in patients over the age of 65[2].
Marketing authorisation date	16 September 2011[4].

2.0 DECISION CONTEXT

2.1 Background

According to data reported by Public Health Wales, the number of patients receiving treatment for HIV or AIDS in Wales in 2009 was 1,193[5]. Further, the Health Protection Agency reported 161 new diagnoses of HIV infection in Wales in 2010[6]. HIV leads to a

reduction in $CD4^+$ lymphocytes of the infected host[7]. Clinical guidelines recommend referring to the patient's $CD4^+$ count as well as the plasma viral load to decide when to begin antiretroviral treatment during HIV infection[8,9]. The choice of any regimen should be guided by the results of resistance testing and other factors, such as the ability of the patient to adhere to and tolerate individual drugs. Therefore, the British HIV Association (BHIVA) guidelines (2008) emphasise that highly active antiretroviral treatment (HAART) regimens must be individualised for patients in order to achieve the maximum potency, durability, adherence and tolerability, whilst avoiding long term toxicities and any likely drug interactions[8]. A HAART regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor is recommended first-line in newly diagnosed HIV-1 patients in whom treatment is deemed appropriate[8].

NNRTIs can be associated with safety and tolerability problems (mainly hepatotoxicity, central nervous system symptoms, and/or rash)[10]. Poor adherence to antiretroviral therapy has been shown to increase the risk of incomplete viral suppression, disease progression and death[11]. 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[2]. Nevirapine has historically been used twice-daily as 200 mg IR tablets[12]. It has been proposed that the use of once-daily dosing with 400 mg 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 200 mg IR nevirapine daily is required[2,8]. This lead-in period has been found to lessen the frequency of rash in patients treated with nevirapine[2].

2.2 Comparators

The comparator requested by the Welsh Medicines Partnership (WMP)* was nevirapine 200 mg IR tablets twice-daily.

2.3 Guidance and related advice

- BHIVA guidelines for the routine investigation and monitoring of adult HIV-1 infected individuals (2011)[15].
- European AIDS Clinical Society. European guidelines for the clinical management and treatment of HIV-infected adults in Europe (2011)[9].
- BHIVA guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy (2008)[8]. At the time of writing, these guidelines are under review.

AWMSG is concurrently considering:

- Nevirapine (Viramune®) 50 mg, 100 mg and 400 mg PR tablets in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adolescents and children three years and above and able to swallow tablets[3].
- Rilpivirine (Edurant®▼) in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml[16].

AWMSG has previously issued a recommendation for the use of the following NNRTI:

- Etravirine (Intelence®▼) for the treatment of HIV-1 infected, antiretroviral treatment-experienced adults in combination with a boosted protease inhibitor and other antiretroviral medicinal products[17].

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

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included results from two randomised trials designed to demonstrate clinical equivalence of nevirapine twice-daily 200 mg IR tablets and nevirapine once-daily 400 mg PR tablets: VERxVE, conducted in treatment-naive patients, and TRANxITION, conducted in treatment-experienced patients[1,13,14].

3.1 Treatment-naive patients: VERxVE study

This multicentre, randomised, double-blind, double-dummy phase III study enrolled treatment-naive HIV-1 infected adults (≥ 18 years) with a baseline viral load ≥ 1,000 RNA copies/ml and a $CD4^+$ count of > 50 to < 400 cells/mm^3 for males and > 50 to < 250 cell/mm^3 for females[13]. Genotypic resistance testing was performed at screening and those with resistance to NNRTIs, tenofovir disoproxil fumarate, emtricitabine or lamivudine were excluded. Eligible patients entered a 14-day lead-in phase of once-daily nevirapine 200 mg IR tablets, during which there were 55 discontinuations (see Section 3.4). Remaining patients (n = 1,013) were then stratified by viral load and randomised 1:1 to nevirapine once-daily 400 mg PR tablets or nevirapine twice-daily 200 mg IR tablets, both in combination with tenofovir disoproxil fumarate and emtricitabine.

Data analysis included all patients who took at least one dose of study drug (n = 1,011). The primary endpoint of sustained virological response (defined as two consecutive measurements of < 50 copies/ml at least two weeks apart) at week 48 was achieved in 409/505 (81.0%) patients that received once-daily nevirapine 400 mg PR and 384/506 (75.9%) patients that received twice-daily nevirapine 200 mg IR, demonstrating non-inferiority of nevirapine 400 mg PR ($p < 0.0001$). This was supported by secondary endpoints including the time to loss of virological response (TLOVR) and $CD4^+$ count at week 48. Treatment compliance, as measured by the return of unused medications by 492 patients that received 400 mg PR and 490 patients that received 200 mg IR, was 99% and 97.6%, respectively. Of the 29 patients without pill-count data, 27 discontinued treatment before week 4. Resistance development was similar between both treatment regimens[13].

3.2 Nevirapine-experienced patients: TRANxITION study

This was a multicentre, open-label, randomised phase III study which enrolled treatment-experienced HIV-1 infected adults (≥ 18 years) with an undetectable viral load (< 50 copies/ml at screening). Eligible patients had received at least 18 weeks of twice-daily nevirapine 200 mg IR with fixed-dose background therapy. Patients (n = 445) were stratified according to their background therapy and randomised 2:1 to receive once-daily nevirapine 400 mg PR tablets or remain on twice-daily nevirapine 200 mg IR tablets[14].

The primary endpoint of the proportion of patients with sustained virological response (defined per the VERxVE study) at week 24 was achieved in 262/295 (88.8%) of patients that received once-daily nevirapine 400 mg PR tablets and 131/148 (88.5%) of patients treated with twice-daily nevirapine 200 mg IR tablets, demonstrating non-inferiority of nevirapine 400 mg PR. This was supported by secondary endpoints including the proportion of patients with sustained virological response (viral load of < 50 copies/ml) at week 48, TLOVR and change in $CD4^+$ count from baseline[14].

3.3 Comparative safety

The safety profile of nevirapine, including rash and severe or life-threatening incidences of skin reaction, hepatoxicity and granulocytopenia, is documented[2]. The company provided 48-week safety data from the VERxVE and TRANxITION studies. The active ingredient used in nevirapine 400 mg 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[18].

In the VERxVE study, during the randomised treatment period, 100/505 (19.8%) patients in the nevirapine 400 mg PR arm experienced investigator-defined drug-related adverse events (AEs), compared with 123/506 (24.3%) in the nevirapine 200 mg IR arm[13]. Discontinuation due to study drug occurred in 32/505 (6.3%) and 45/506 (8.9%) in the PR and IR arms, respectively. The most commonly cited AE for discontinuation was rash; however, incidence of rash and discontinuations caused were balanced between treatment arms. Hepatic events were reported in 28/505 (5.5%) of patients randomised to nevirapine 400 mg PR and 46/506 (9.1%) of patients randomised to nevirapine 200 mg IR. No deaths were deemed attributable to study drug[13].

In the TRANxITION study, 41/295 (13.9%) patients in the nevirapine 400 mg PR arm experienced investigator-defined drug-related AEs, compared with 5/148 (3.4%) in the nevirapine 200 mg IR arm[14]. AEs were numerically higher for nevirapine 400 mg PR in all five system organ classes examined. Discontinuation due to study drug occurred in 7/295 (2.4%) and 1/148 (0.7%) in the respective groups. No life-threatening or fatal events occured[14].

3.4 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[18].
- CHMP conclude that no new safety signals were observed with the use of nevirapine 400 mg PR tablets[18]; however, a difference in the frequency of AEs was observed between the treatment arms in the TRANxITION study. CHMP accept that this may be due to a reporting bias in favour of the more familiar nevirapine 200 mg IR treatment as a result of the open-label nature of the trial and acknowledge that this difference was not observed in the double-blind VERxVE study[18]. Further, AEs categorised as Division of Acquired Immunodeficiency Syndrome (DAIDS) grade 3 or 4 occurred at similar rates: 6.4% versus 6.1% in the PR and IR groups, respectively[14].
- Nevirapine 400 mg PR tablets have been developed with the aim of increasing patient convenience and therefore adherence. In the VERxVE study, compliance was shown to be comparable between the use of nevirapine 400 mg PR and nevirapine 200 mg IR[13]. Pill counts have, however, not been considered as robust for some time[19], 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[20]. No compliance data were provided for the TRANxITION study.
- There were 55 discontinuations during the nevirapine 200 mg IR lead-in phase of the VERxVE study; 38 (69.1%) of these were due to an AE, mostly rash[13]. Although the use of nevirapine 200 mg IR tablets is outside the scope of this appraisal, this is clinically relevant as nevirapine-naive patients will require this lead-in phase prior to receiving nevirapine PR.

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 has highlighted controlled trials demonstrating non-inferiority of the PR and IR formulation tablets in adults in terms of viral response (see Section 3.0)[1]. CHMP confirms that comparable bioavailability and exposure was demonstrated between the IR and PR formulations[18].
- 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.

Drug	Regimen	Cost per patient per year
Viramune® (nevirapine) 400 mg PR tablets	400 mg once daily	£2,068
Viramune® (nevirapine) 200 mg IR tablets	200 mg twice daily	£2,068
Viramune® (nevirapine) 50 mg per 5 ml oral suspension	20 ml twice daily	£3,066
Costs are based on MIMS list prices[21]. *See relevant Summaries of Product Characteristics (SPCs) for full dosing details[2,12,22].* *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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