CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-976

MICROBIOLOGY REVIEW

DIVISION OF ANTIVIRAL PRODUCTS
OFFICE OF NEW DRUGS
MICROBIOLOGY REVIEW
NDA: 21-976 **SN**: 000 **DATE REVIEW COMPLETE:** 06/19/2006
Microbiology Reviewer: Lisa K. Naeger, Ph.D.

NDA#: 21-976 **Serial #:** 000
Reviewer's Name: Lisa K. Naeger, Ph.D.

Sponsor's Name and Address: Tibotec-Virco, USA
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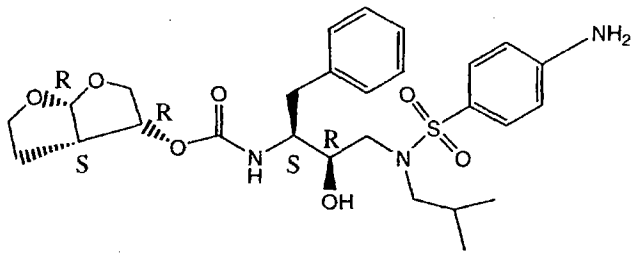
Amendments:
Related/Supporting Documents: IND62477

Product Name(s)
Proprietary: PREZISTA/rtv
Non-Proprietary/USAN: Darunavir/rtv; darunavir, TMC114
Code Name/Number:

Empirical formula: $C_{27}H_{37}N_3O_7S \cdot C_2H_5OH$
Chemical Name: {3-[(4-amino-benzenesulfonyl)-isobutyl-amino]- 1 -benzyl-2-hydroxy-propyl} -carbamic acidhexahydro-furo-[2,3-b]furan-3-yl ester.ethanolate

Molecular mass: Relative molecular mass: 547.656 (active moiety) + 46.068 (ethanol, EtOH) = 593.724 (TMC 11 4-ethano late)

Structural Formula:



Darunavir

DIVISION OF ANTIVIRAL PRODUCTS
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MICROBIOLOGY REVIEW
NDA: 21-976 **SN**: 000 **DATE REVIEW COMPLETE:** 06/19/2006
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Drug category: antiviral for HIV infection
Dosage Form(s): Oral; *co-administration of ritonavir as 100-mg soft gelatin capsules*
Route(s) of Administration: Oral
Indication(s): Combination antiretroviral treatment of HIV-1 infected adult subjects with evidence of viral replication who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

Dispensed: Rx _X_ OTC___

Abbreviations: ABC, abacavir; APV, amprenavir; ATV, atazanavir; AZT, zidovudine; Control, comparator PI arm; ddI, didanosine; d4T, stavudine; DLV, delavirdine; EFV, efavirenz; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus-1; IC, inhibitory concentration; IDV, indinavir; LAM, lamivudine; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background therapy; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; /rtv, ritonavir-boosted; RT, reverse transcriptase; SQV, saquinavir; ENF, enfuvirtide; TNF, tenofovir; TPV, tipranavir

EXECUTIVE SUMMARY

Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles. Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir,or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine,, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, efavirenz , or nevirapine, and the fusion inhibitor enfuvirtide.

Resistance
Cell Culture: HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir/ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV had 6- to 21-fold decreased susceptibility to darunavir and harbored 3 to 6 of the following amino acid substitutions S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains

harboring multiple protease inhibitor resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, including L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease mutations and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 nM

Clinical studies of darunavir/ritonavir in treatment-experienced subjects: In the Phase 2 trials Studies C202, C213 and C215, multiple protease inhibitor-resistant HIV-1 isolates from highly treatment-experienced subjects who received 600/100 mg darunavir/rtv b.i.d. and experienced virologic failure, either by rebound, or by never being suppressed, developed amino acid substitutions that were associated with a decrease in susceptibility to darunavir. The amino acid substitution V32I developed on darunavir/rtv 600/100 mg b.i.d. in greater than 30% of virologic failure isolates and substitutions at amino acid I54 developed in greater than 20% of virologic failure isolates. Other substitutions that developed in 10% to 20% of darunavir/rtv virologic failure isolates occurred at amino acid positions I15, L33, I47, G73 and L89. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 21-fold at baseline and 94-fold at failure.

Cross-resistance

Darunavir has a <10-fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most protease inhibitors remain susceptible to darunavir. In Studies C202 and C213, 60% (24/40) of subjects with decreased susceptibility to tipranavir (fold change >3) at baseline demonstrated a 1 log_{10} decrease from baseline at week 24 on darunavir/rtv and 45% (18/40) achieved <50 copies/mL serum HIV RNA levels. In Study C215, 60% (64/107) of subjects with resistance to tipranavir (>3-fold change) at baseline achieved a 1 log_{10} decrease from baseline at week 24 on darunavir/rtv and 33% (35/107) achieved <50 copies/mL serum HIV RNA levels.

Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from protease inhibitor-resistant viruses showed a fold change in EC_{50} values <3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. Of the viruses isolated from subjects experiencing virologic failure on darunavir/ritonavir 600/100 mg b.i.d., greater than 50% were still susceptible to tipranavir while less than 5% were susceptible to other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir).

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors or the fusion inhibitor is unlikely because the viral targets are different.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of 600/100 mg b.i.d darunavir/rtv therapy. As-treated analyses were conducted to evaluate the impact of specific baseline protease inhibitor resistance-associated mutations and the number of protease inhibitor resistance-associated mutations at baseline on virologic response. Both specific mutations and the number of baseline mutations as well as susceptible drugs in the optimized background regimen and enfuvirtide use affected darunavir/rtv response rates in Phase 2 Studies C202 and C213.

The presence at baseline of the mutations V32I, I47V, or I54L or M, was associated with a decreased virologic response to darunavir and decreased susceptibility to darunavir. In addition, a diminished virologic response was observed in subjects with ≥7 protease inhibitor resistance-associated mutations (any change at amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, or 90) at baseline. The response rate in all subgroups (by type and number of mutations at baseline) was generally higher in the darunavir/rtv group compared to the control group.

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Analyses showed that response rates at Week 24 decreased when the baseline darunavir phenotype was >7-fold. Phenotypic subgroups of 0-2, >2-7, >7-30 and >30 described responses rates in four tiers of 88%, 73%, 52% and 43% with a 1 $\log_{10}$ decrease from baseline, respectively, and 60%, 47%, 24% and 19% with <50 copies/mL, respectively.

The number of susceptible drugs in the optimized background regimen and enfuvirtide use affected darunavir/rtv response rates. In Studies C202 and C213, subjects with no susceptible NRTIs at baseline had lower response rates (38% with 1 $\log_{10}$ decrease and 13% with <50 copies/mL) than those with at least one susceptible NRTI. In addition, for subjects with baseline darunavir phenotypes of >10 in studies C202, C213 and C215, response rates were 81% (13/16) when ENF was used for the first time concomitantly with darunavir while response rates were 36% (27/74) for those who did not use ENF concomitantly.

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