PDL DRUG REVIEW

Proprietary Name: Pifeltro®
Common Name: doravine
PDL Category: Antiretrovirals

Comparable Products	Preferred Drug List Status
Edurant	Preferred
Sustiva	Preferred

Summary

Pharmacology/Usage: Doravirine, the active ingredient of Pifeltro®, is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI). It inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase.

Indication: In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults with no prior antiretroviral treatment history.

There is no pregnancy category for this medication; however, the risk summary indicates that no adequate human data are available to establish if Pifeltro® poses a risk to pregnancy outcomes. In animal studies, no adverse developmental effects were seen when treatment was used at higher than normal human doses. There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to Pifeltro® during pregnancy. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-Coated Tablets: 100mg

Recommended Dosage: Take one tablet once daily, with or without food. If co-administered with rifabutin, increase the Pifeltro® dose to one tablet BID for the duration of rifabutin co-administration.

Dose adjustments are not required with renal impairment or with mild to moderate hepatic impairment. However, use has not been adequately studied in patients with end-stage renal disease, in dialysis patients, and in patients with severe hepatic impairment.

Drug Interactions: Refer to the contraindications section for a comprehensive list of drugs contraindicated with Pifeltro®. Concomitant use of rifabutin with doravirine can decrease doravirine levels. It is recommended to increase Pifeltro® dosage to one tablet BID with concomitant use. Concomitant use of Pifeltro® with efavirenz, etravirine, and nevirapine is not recommended.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Pifeltro® + 2 NRTIs) minus reported % incidence for darunavir + ritonavir + 2 NRTIs in the DRIVE-FORWARD study. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its*

comparator. The most frequently reported adverse events included nausea (0%), headache (3%), fatigue (3%), diarrhea (0%), abdominal pain (3%), dizziness (1%), rash (0%), abnormal dreams (<1%), insomnia (0%), and somnolence (0%). Laboratory abnormalities included total bilirubin: 1.1- <1.6 X ULN (4%) or 1.6- <2.6 x ULN (>1%) or ≥2.6 x ULN (0%); creatinine : >1.3-1.8 x ULN or increase of >0.3mg/dl above baseline (0%) or >1.8 x ULN or increase of ≥1.5 above baseline (0%); aspartate aminotransferase: 2.5- <5.0 x ULN (1%) or ≥5.0 x ULN (0%); alanine aminotransferase: 2.5- <5.0 x ULN (1%) or ≥5.0 x ULN (0%); alkaline phosphatase: 2.5- <5.0 x ULN (0%) or ≥5.0 x ULN (0%); and creatine kinase: 6- <10 x ULN (0%) or ≥10 x ULN (0%).

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. Autoimmune disorders, such as Graves' disease, polymyositis, and Guillain-Barre syndrome, have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after start of treatment.

Contraindications: When co-administered with drugs that are strong CYP3A enzyme inducers, which may decrease the effectiveness of Pifeltro®, including but not limited to: Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), the androgen receptor inhibitor enzalutamide, antimycobacterials (rifampin, rifapentine), mitotane, and St. John' wort.

Manufacturer: Merck Sharp & Dohme

Analysis: The efficacy of Pifeltro® is based on the analyses of 48-week data from 2 randomized, multicenter, double-blind, active-controlled, phase 3 trials (DRIVE-FORWARD and DRIVE-AHEAD) that included HIV-1 infected subjects with no antiretroviral treatment history (N=1494).

In DRIVE-FORWARD, subjects (N=766) were randomized and received at least 1 dose of either Pifeltro® or darunavir 800mg plus ritonavir 100mg (DRV+r), each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years, 16% were female, 27% were non-white, 4% had hepatitis B and/or C virus co-infection, 10% had a history of AIDS, 20% had HIV 1 RNA >100,000 copies/ml, and 86% had CD4+ T-cell count >200 cells/mm^3. Results suggested that the mean CD4+ T-cell counts in the Pifeltro® and DRV+r groups increased from baseline by 193 and 186 cells/mm^3, respectively.

In DRIVE-AHEAD, subjects (N=728) were randomized and received at least 1 dose of either Delstrigo® (doravirine, lamivudine [3TC], & tenofovir DF [TDF] combination) or efavirenz (EFV) 600mg/FTC 200mg/TDF 300mg. At baseline, the median age was 31 years, 15% were female, 52% were non-white, 3% had hepatitis B or C co-infection, 14% had a history of AIDS, 21% had HIV-1 RNA >100,000copies/ml, and 88% had CD4+ T-cell count >200cells/mm^3. Results suggested that the mean CD4+ T-cell counts in the Delstrigo® and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm^3, respectively.

Results of the study can be seen in the table below, which was adapted from the prescribing information.

Outcome	DRIVE-FORWARD		DRIVE-AHEAD	
	Pifeltro® +2 NRTIs QD	DRV+r +2 NRTIs QD	Delstrigo® QD	EFV/FTC/TDF QD
	N=383	N=383	N=364	N=364
HIV-1 RNA <50 copies/ml	84%	80%	84%	81%
Treatment Differences	3.9%		3.5%	
HIV-1 RNA ≥50 copies/ml	11%	13%	11%	10%
No virologic data at week 48 window	5%	7%	5%	9%
Discontinued study due to adverse event or death	1%	3%	2%	7%

Outcome	DRIVE-FORWARD		DRIVE-AHEAD	
	Pifeltro® +2 NRTIs QD	DRV+r +2 NRTIs QD	Delstrigo® QD	EFV/FTC/TDF QD
	N=383	N=383	N=364	N=364
Discontinued study for other reasons	3%	4%	2%	2%
On study but missing data in window	<1%	<1%	0	<1%
Proportion (%) of subjects with HIV-1 RNA <50copies/ml at week 48 by baseline & demographic category				
Gender: Male	84% (N=319)	82% (N=326)	84% (N=305)	80% (N=311)
Gender: Female	81% (N=64)	67% (N=57)	85% (N=59)	83% (N=53)
Race: White	87% (N=280)	83% (N=280)	84% (N=177)	81% (N=170)
Race: Non-White	75% (N=103)	73% (N=103)	84% (N=187)	80% (N=194)
Ethnicity: Hispanic or Latino	88% (N=93)	81% (N=86)	83% (N=126)	84% (N=120)
Ethnicity: Not Hispanic/Latino	82% (N=284)	79% (N=290)	85% (N=236)	79% (N=238)
NRTI background: FTC/TDF	83% (N=333)	81% (N=335)	-	-
NRTI background: ABC/3TC	86% (N=50)	75% (N=48)	-	-
Baseline HIV-1 RNA: ≤100,000 copies/ml	86% (N=300)	81% (N=308)	86% (N=291)	83% (N=282)
Baseline HIV-1 RNA: >100,000 copies/ml	77% (N=83)	74% (N=74)	77% (N=73)	72% (N=82)
CD4+ T-cell count: ≤200 cells/mm^3	81% (N=42)	66% (N=67)	66% (N=44)	78% (N=46)
CD4+ T-cell count: >200 cells/mm^3	84% (N=341)	83% (N=316)	87% (N=320)	81% (N=318)

Place in Therapy: Pifeltro® is an oral tablet indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults with no prior antiretroviral treatment history. In a clinical study, Pifeltro® in combination with 2 NRTIs was as effective as darunavir plus ritonavir in combination with 2 NRTIs for achieving HIV-1 RNA <50copies/ml.

In the DRIVE trials of treatment-naïve people with HIV, Pifeltro® was shown to be non-inferior to boosted darunavir in terms of virologic efficacy at 48 weeks with no significant differences across subgroups. In a 96-week extension (not yet published), Pifeltro® was associated with a higher rate of viral suppression than boosted darunavir, although there was no difference in patients with high baseline viral load. In these studies, Pifeltro® had a favorable lipid profile compared to boosted darunavir. While Pifeltro® may have advantages over boosted darunavir in certain patients, there is no evidence that it is safer or more effective than the currently available, more cost-effective medications. It is therefore recommended that Pifeltro® be added to the Recommended Drug List as non-recommended.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended**

References

[1] Pilfeltro [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; 2018.