CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-003/SE1-002

21-004/SE1-002

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA # 21,003; SE1-002
NDA # 21,004; SE1-002

REVIEWER : LALJI MISHRA, Ph.D.
CORRESPONDENCE DATE : 02/27/01
CDER RECEIPT DATE : 02/28/01
REVIEW ASSIGN DATE : 03/08/01
COMPLETION DATE : 08/13/01

SPONSOR: Glaxo Smith Kline
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SUBMISSION REVIEWED: SE1-002; SE1-002/N (07/09/01); SE1-002/BL (07/09/01)

DRUG CATEGORY: Antiviral

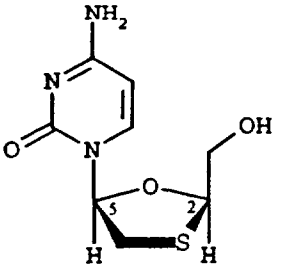
INDICATION: Treatment of Hepatitis B infection in pediatric patients

DOSAGE FORM: Tablets and Oral Solution

PRODUCT NAMES:

a. PROPRIETARY: Epivir^{R}
b. NON-PROPRIETARY: Lamivudine
c. CHEMICAL: (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one

STRUCTURAL FORMULA



BACKGROUND

Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. It inhibits the reverse transcriptase (RT) and DNA polymerase activities of hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1)). Lamivudine has been demonstrated to exhibit antiviral activity against HBV both in vitro and in vivo (Dienstag et al., 1999). The IC_{50} values (the concentration of drug needed to reduce the level of extracellular HBV DNA by 50%) of lamivudine varied from 0.01 μM (2.3 ng/mL) to 5.6 μM (1.3 μg/mL) depending upon the duration of exposure of the cells, the cell model system, and the protocol used.

HBV mutants with reduced susceptibility to lamivudine have been obtained from patients receiving long term therapy. Genotypic analysis showed that these isolates contain amino acid substitution in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV reverse transcriptase. This site is involved in the nucleotide binding of the catalytic domain of reverse transcriptase. HBV mutants contain a substitution of valine or isoleucine for the methionine at position 552 (M552V or M552I)) in the YMDD motif of the reverse transcriptase (Ling et al., 1996; Allen et al., 1998; Melagari et al., 1998; Ono-Nita et al., 1999). The mutations M552V is most frequently accompanied by a substitution of methionine for leucine at position 528 (L528M). Mutation L528 lies in the B domain of HIV-1 reverse transcriptase.

Lamivudine (Epivir-HBV) Tablets and Oral solution were approved on December 8, 1998 by the FDA for the treatment of HBV infection in adults. Glaxo Smith Kline (GSK) has filed supplemental new drug applications sNDA, 21-003 & 21-004 to provide results from pediatric clinical studies and seeks marketing approval of lamivudine tablets and oral solution for the treatment of HBV infection in pediatric patients 2 to 17 years of age. In the current application, GSK has submitted results of two studies: NUCB 2020 (dose ranging and pharmacokinetic study in children and adolescents) and NUC30903 (safety and efficacy study in pediatric patients).

Microbiology data for the study NUC30903 pertaining to genotypic resistance are reviewed here.

PROTCOL

NUC30903: A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of 52 of weeks lamivudine treatment at a dose of 3 mg/kg in pediatric subjects with chronic hepatitis B.

Objectives

Primary

1. To compare the efficacy of lamivudine versus placebo in children with chronic hepatitis B.
2. To compare the safety of lamivudine versus placebo in children with chronic hepatitis B.

Study Design

NUC30903 was a randomized, double-blind, placebo-controlled, international study, designed to evaluate the safety and efficacy of 52 weeks of lamivudine treatment at a dose of 3 mg/kg once daily in pediatric subjects with chronic hepatitis B. This study utilized baseline biopsies for disease staging purposes but did not require follow-up liver biopsies. The study population comprised male and female subjects 2 to 17 years old with chronic HBV infection.

Microbiologic Specific Inclusion Criteria

1. Presence of hepatitis B surface antigen (HBsAg) in serum for at least 6 months.
2. Presence of hepatitis B e antigen (HBeAg) at the time of screening.
3. Positive (≥ 0.7 MEq/mL) for hepatitis B viral DNA (HBV DNA) by [redacted] assay at time of screening.
4. Mean ALT raised to ≥1.3x upper limit of reference range (established by the mean of one determination ≥3 months before screening, and the screening value).
5. All ALT values must have been <500 IU/mL.
6. Liver biopsy material/slides taken within the previous 24 months, and ≥6 months post interferon treatment. A biopsy may have been performed between the screening and baseline (randomization visits).

Microbiologic Specific Exclusion Criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. Interferon treatment within the previous 12 months; anti-infective or immunomodulatory treatment within the previous 6 months.
2. HBeAb positive.
3. Co-infection with HIV (human immunodeficiency virus), HCV (hepatitis C virus), or HDV (hepatitis D virus).
4. Recipient of systemic antiviral therapy (with the exception of prophylaxis or treatment for influenza), immunomodulators, systemic cytotoxic agents, or systemic corticosteroids within 6 months prior to study screening.
5. History of hypersensitivity to nucleoside analogues.

End Points

Primary

The primary efficacy measure of complete virologic response (CVR) was a composite measure consisting of loss of serum HBeAg and reduction of serum HBV DNA to undetectable levels.

HBV DNA

The levels of HBV DNA in serum were measured using the signal amplification branch DNA (bDNA) [redacted] assay. Levels were measured at screening, baseline, and weeks 4, 8, 16, 24, 32, 40, 48 and 52.

HBeAg

The presence/absence of hepatitis B e antigen (HBeAg) was measured using the HBe (rDNA) [redacted] The presence/absence was measured at screening, baseline, and weeks 4, 8, 16, 24, 32, 40, 48 and 52.

Secondary

ALT

Serum ALT was measured at screening, baseline, and Weeks 4, 8, 16, 24, 32, 40, 48 and 52.

The proportion of subjects with sustained ALT response (defined as at least 2 consecutive ALT measurements $\leq$1.0 x ULN and maintained through to week 52, without any measurements >ULN) was compared between the treatment groups.

HBV Serologic Markers

HBV serologic markers were measured for the assessment of the secondary endpoint. These include HBeAg, HBeAb, HBsAg and HBsAb.

HBeAg/HBeAb

The presence/absence of HBeAg and HBeAb were measured using the HBe (rDNA) [redacted] The presence/absence was measured at screening, baseline, and Weeks 4, 8, 16, 24, 32, 40, 48 and 52.

HBsAg/HBsAb

The presence/absence of hepatitis B s antigen (HBsAg) and hepatitis B s antibody (HBsAb) were measured using the [redacted] respectively. HBsAg was measured at screening, baseline, Weeks 32, and 52. HBsAb was only measured if subject experienced loss of HBsAg.

Other Viral Markers

The following serologic assays were performed at screening visit only:

[redacted]

SUMMARY

I. Pre-therapy and Post-therapy Viral Load

The mean and median baseline viral load of patients enrolled in the study NUC 30903 are presented by treatment group in Table 1. In addition, all patients had detectable HBeAg and HBsAg at baseline. Data shown in Table 1 are derived from NDA 21003, vol 8.4, page 141, Table 9. Results of complete virologic response (CVR) at week 52 of lamivudine treatment are shown in Table 2. Twenty-three percent of lamivudine treated patients showed CVR. However, 13% of the patients treated with placebo also exhibited CVR at week 52. Results of HBV DNA response at week 52 are shown in Table 3. There was a highly significant difference between the number of placebo-treated (16%) and lamivudine-treated patients (61%) with an HBV DNA response at week 52. These data (Table 3) were derived from NDA 21003, vol 8.4, page 196, Table 35.

Table 1: Baseline serum HBV DNA levels

	Treatment Groups			
	Placebo (n = 95)		Lamivudine (n = 191)	
	Median (range)	Mean	Median (range)	Mean
HBV DNA (MEq/mL)	1032 [redacted]	1884.0	895 [redacted]	2145.1

Table 2: Complete virologic response at week 52

	Treatment Group	
	Placebo (n = 95)	Lamivudine (n = 191)
Response at week 52	N (%)	N (%)
Complete virologic response*	12 (13)	44(23)
Non/Partial virologic response	83 (87)	147(77)

* Complete virologic response was defined as loss of detectable HBeAg in serum and reduction of HBV DNA in serum to undetectable level (<0.7MEq/mL)

Table 3: HBV DNA response at week 52

	Treatment Groups	
HBV DNA response* at week 52	Placebo (n = 95)	Lamivudine (n = 191)
	15 (16%)	117 (61%)

* HBV DNA response is defined as HBV DNA below the lower limit of detectability

II. **HBV Serological markers**

II (a). **HBeAg seroconversion (2 component)**

The number of patients, at week 52, with 2 component HBeAg seroconversion (HBeAg-ve/HBeAb+ve) was 14/95 (15%) for the placebo and 48/191 (25%) for the lamivudine treatment group.

II (b). **HBeAg loss**

The number of patients achieving HBeAg loss at week 52 for the placebo-and lamivudine-treated patients was 14/95 (15%) and 50/191 (26%), respectively.

II (c). **HBsAg loss**

Three (3/191, 2%) patients of the lamivudine treatment group demonstrated HBsAg loss during the 52 week of this study.

III. **Genotypic analysis**

Genotypic analysis of HBV isolates was performed for all subjects with serum available at baseline and Week 52 or at the end of treatment/study withdrawl, [redacted] Genotypic assay is described in Methodology section of this review. A summary of incidence of YMDD variant HBV is presented in Table 4.

Table 4: Incidence of YMDD HBV mutations at Week 52

	Treatment Group	
	Placebo (n = 96)	Lamivudine (n = 191)
	N (%)	N (%)
Genotype outcome Assessed	86 (90)	166(87)
YMDD Variant at week 52	1 (1)	30 (18)
Mixed	0	19 (63)
Full	1 (100)	11 (37)
Non-Variant at week 52	85 (99)	136 (82)
Wild-type	78 (92)	84 (62)
HBV DNA-ve(PCR)	7 (8)	52 (38)

The incidence of HBV variant with YMDD mutations at week 52 was 30/166 (18%) for subjects in the lamivudine-treatment group. The incidence of fully variant (>95% of viral DNA showing evidence of YMDD variant) and mixed (between 5% and 95% of viral DNA showing evidence of YMDD variant) populations, were 11/30 (37%) and 19/30 (63%) respectively. One subject in the placebo-treatment group had YMDD mutations. However, further investigation revealed that this serum sample was mislabeled inadvertently at the time of blood drawing, and came from a patient treated with lamivudine.

Fifty-two of 136 serum samples from lamivudine-treated patients were DNA-ve (DNA not amplified to a sufficient level for genotypic analysis).

IV (a). **Changes in HBV DNA levels in Subjects with YMDD Mutants and Non-variants HBV**

Median change in serum HBV DNA levels from baseline to week 52 (study visits) for subjects with variant and non-variant HBV are presented in Table 5. These data are from Table 70; NDA 21003, vol 8.4, pages 251-253). For analysis purposes, serum samples with non-detectable HBV DNA were assigned a positive value of 0.35 MEq/mL, half of the detection threshold of the bDNA assay LLOD of 0.7 MEq/mL. The median HBV DNA was 0.35 MEq/mL (undectetable) for the non-variant group from week 8 through 52. Similarly, for weeks 8 through 40, the HBV DNA was undetectable in serum of subjects with YMDD variants. However, the median HBV DNA level in the variant group increased to 1.4 MEq/mL at week 48, and to 2.7 MEq/mL at week 52. Overall median HBV DNA values were substantially reduced in both the variant (2.7 MEq/ml) and non-variant (0.35 MEq/mL) groups at week 52, and were below the levels for the placebo group (538 MEq/mL).

Table 5: HBV DNA (MEq/mL) in non-variant and YMDD variant HBV mutants by week of study

YMDD Status	N	Visit	N	Median	Min	Max
Non-Variant	136	Baseline	136	776.8		
		Week 4	133	0.70		
		Week 8	135	0.35		
		Week 16	131	0.35		
		Week 24	134	0.35		
		Week 32	131	0.35		
		Week 40	133	0.35		
		Week 48	136	0.35		
		Week 52	136	0.35		
Variant	30	Baseline	30	1626.00		
		Week 4	29	1.30		
		Week 8	29	0.35		
		Week 16	29	0.35		
		Week 24	29	0.35		
		Week 32	29	0.35		
		Week 40	29	0.35		
		Week 48	28	1.40		
		Week 52	29	2.70		

IV (b). **HBV DNA Response at week 52 in patients with Non-variant and HBV mutants**

The proportions of subjects with an HBV DNA response at week 52 (defined as a decrease in HBV DNA to an undetectable level from a detectable level at baseline) are presented in Table 6.

Table 6: HBV DNA response at week 52 in non-variant and HBV mutants

	Comparison Group	
	Non-Variant (N=136)	Variant (N=30)
	N (%)	n (%)
HBV DNA Response at Week 52	94 (69)	9 (30)
HBV DNA Positive at Week 52	42 (31)	21 (70)

In the HBV variant group, 9/30 (30%) of subjects had an HBV DNA response at week 52 (HBV DNA detectable by PCR, but undetectable by conventional bDNA assay).

IV (c). **Changes in HBV serological markers in patients with non-variant and YMDD HBV mutants**

The number of non-variant subjects that achieved 2 component seroconversion at week 52 was 43/136 (32%). One patient with YMDD mutant HBV (1/30) achieved 2 component seroconversion (loss of HBeAg and gain of HBeAb). One subject with detectable YMDD variant HBV had HBeAg loss at week 52 (1/30 (3%). The rate of HBeAg loss for the non-variant group was 44/136 (32%).

V. **HBV DNA breakthrough and its correlation with the emergence of YMDD mutations**

The purpose of this study was to correlate the emergence of YMDD HBV mutants with HBV DNA breakthrough in pediatric patients enrolled in NUC30903. An HBV DNA breakthrough was defined as two consecutive positive results for HBV DNA (or one positive result if at last visit) after two consecutive negative results in a study patient who was HBV DNA positive at baseline, with the week 52 visit (or last study visit) also positive. The breakthrough HBV DNA levels, YMDD analyses along with HBeAg status of lamivudine treated patients is presented in Table 7. Data presented in Table 7 are derived from Appendix 1, NDA 21003, vol 8.14, pages 32-43.

Matched baseline and breakthrough HBV DNA levels at week 52 with corresponding YMDD analysis data were available for 37 pediatric patients enrolled in NUC903 (Table 7). Of these, isolates from 18 patients (18/37, 49%) had YMDD mutations at week 52. The HBV DNA breakthrough levels for these patients at week 52 ranged from [redacted] It should be noted that not all patients with HBV DNA breakthrough had YMDD mutations.

VI. **Loss of HBsAg and its correlation with HBV DNA and YMDD mutations in lamivudine treated patients**

HBsAg, HBsAb, HBeAg, HBeAb levels, HBV DNA levels and YMDD mutation were measured at different times for patients who were initially enrolled in NUC30903 [redacted]

Subject number	Visit Type	HBV DNA MEq/mL	HBeAg status	YMDD Variant status
35984	Baseline	1648	P	WT
	Week 52	103.9	P	MX
35986	Baseline	2797	P	WT
	Week 52	305.9	P	RES YMDD
35995	Baseline	2079	P	WT
	Week 52	2.7	P	MX
36027	Baseline	225.1	P	WT
	Week 52	56.9	P	RES YMDD
36083	Baseline	26.2	P	WT
	Week 52	0.7	N	0(NI)
36084	Baseline	583.7	P	WT
	Week 52	598.6	P	MX
36133	Baseline	347.2	P	WT
	Week 52	1.5	N	0(NI)
36176	Baseline	1729	P	WT
	Week 52	920.7	P	WT
36189	Baseline	4892	P	WT
	Wee 52	1.2	P	WT
36191	Baseline	262.2	P	WT
	Week 52	1.9	P	MX
36228	Baseline	251.3	P	WT
	Week 52	25.4	P	MX
36334	Baseline	976.8	P	WT
	Week 52	0.7	P	WT
36337	Baseline	8852	P	WT
	Week 52	1.1	P	WT
37397	Baseline	3339.4	P	WT
	Week 52	4	P	WT
37428	Baseline	367.9	P	WT
	Week 52	10.8	P	MX
37437	Baseline	679.2	P	WT
	Week 52	0.7	P	MX
37440	Baseline	537.7	P	WT
	Week 52	192.4	P	RES YMDD
37843	Baseline	28300	P	WT
	Week 52	1.2	P	WT
37870	Baseline	3396		WT
	Week 52	707.5	P	RES YMDD
37959	Baseline	152.8	P	WT
	Week 52	1.7	N	WT

WT = Wild type, RES = resistant YMDD HBV, MX = mixed wild type and resistant virus, 0 = undetectable, NI = No inhibition

Table 7: Patient/Visit Profile for HBV DNA Breakthrough

Subject number	Visit Type	HBV DNA MEq/mL	HBeAg status	YMDD Variant status
34869	Baseline	76.4	P	WT
	Week 52	1	P	WT
35107	Baseline	2518.7	P	
	Week 52	1018.8	P	WT
35115	Baseline	311.3	P	WT
	Week 52	1.8	P	WT
35196	Baseline	452.8	P	WT
	Week 52	6.2	P	
35258	Baseline	1499.9	P	WT
	Week 52	2603.6	P	WT
35326	Baseline	2094.2	P	WT
	Week 52	1.2	P	WT
35439	Baseline	3679	P	WT
	Week 52	735.8	P	WT
35443	Baseline	2264	P	WT
	Week 52	1216.9	P	RES YMDD
35532	Baseline	4810	P	WT
	Week 52	304.8	P	MX
35542	Baseline	537.4	P	WT
	Week 52	313.4	P	RES YMDD
35552	Baseline	2859	P	WT
	Week 52	2.1	P	MX
35626	Baseline	339.6	P	WT
	Week 52	0.9	P	WT
35676	Baseline	3396	P	WT
	Week 52	67.9	P	WT
35734	Baseline	10610	P	WT
	Week 52	2.9	P	WT
35740	Baseline	178.7	P	WT
	Week 52	14.3	P	WT
35876	Baseline	2.2	P	WT
	Week 52	1.1	P	WT
35978	Baseline	6629	P	WT
	Week 52	160.5	P	RES YMDD
35980	Baseline	549.8	P	WT
	Week 52	0.8	N	RES YMDD
35981	Baseline	1604	P	WT
	Week 52	119.5	P	RES YMDD

Table 8: HBsAg Loss in a subject 38609 participating in NUC30903

Subject #	Visit	HBeAg	HBeAb	HBsAg	HBsAb	HBV DNA	YMDD
38609	Baseline NUC 30903	P	N	P		1981	
38609	Week 4	P	N			<0.7	
38609	Week 32	P	N	P		<0.7	
38609	Week 48	P	N			<0.7	
38609	Week 52 baseline NUC309 26	P	N	P		<0.7	
38609	Month 1	P	N			2.5	
38609	Month 2	P	N			1.4	
38609	Month 3	P	N			53.8	
38609	Month 6	P	N	P		481.1	RES YMDD
38609	Month 9	P	N			396.2	
38609	Early w/d	P	N	N	N	311.3	MX

CONCLUSIONS

With respect to microbiology, this sNDA is supported. Results from NUC30903 showed that 23% of lamivudine treated pediatric patients had complete virologic response as compared to 13% on placebo. Similarly, 61% of the patients on lamivudine treatment at week 52 had HBV DNA below the lower limit of assay detectability (<0.7 MEq/mL). Approximately, 25% of patients on lamivudine treatment were HBeAg negative and HBeAb positive at week 52.

Genotypic analysis showed that HBV isolates from 18-19% patients receiving lamivudine treatment for 52 weeks harbored YMDD mutations M552V or M552I in HBV reverse transcriptase gene. YMDD mutations, M552V or M552I along with the mutation L528M confer reduced susceptibility to lamivudine in vivo and in vitro (Ling et al., 1996; Allen et al., 1998; Melagari et al., 1998; Ono-Nita et al., 1999). The mutation L528 M has been only detected in HBV variants with the YMDD mutations (Gauthier et al., 1999; Ono-Kioka et al., 2001). The L528M is a compensatory mutation, and restored the replication capability of the M552V mutations (Fu & Cheng, 1998; Ono et al., 2001). A relatively lower percentage of patients with YMDD mutations exhibited a complete HBV response at week 52 compared to patients containing wild-type HBV.

HBV DNA breakthrough (increase in HBV DNA after reaching <0.7 MEq/ml) at week 52 was reported for 39 patients enrolled in NUC30903. Genotypic analysis of matched baseline and week 52 isolates from 37 patients showed that isolates from 18 patients (18/37, 49%) had YMDD mutations at week 52. The HBV DNA levels for these patients at week 52 ranged from [redacted] Since YMDD mutations were detected in 49% of patients with HBV DNA breakthrough, it is likely that besides YMDD mutations, other factors, i.e., plasma concentrations, adherence, immune status of the patients may be contributing towards HBV DNA breakthrough.

[redacted]

METHODOLOGY

[redacted]

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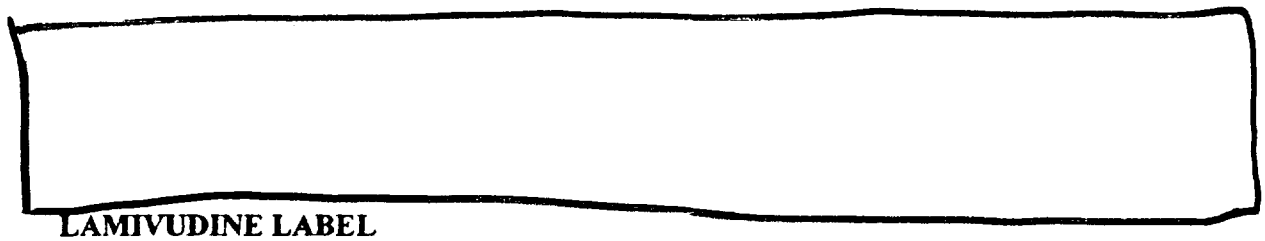

LAMIVUDINE LABEL

MICROBIOLOGY :

Mechanism of Action: Lamivudine is a synthetic nucleoside analogue. Lamivudine is phosphorylated intracellularly to lamivudine triphosphate, L-TP. Incorporation of the monophosphate form into viral DNA by hepatitis B virus (HBV) polymerase results in DNA chain termination. L-TP also inhibits the RNA- and DNA-dependent DNA polymerase activities of HIV-1 reverse transcriptase (RT). L-TP is a weak inhibitor of mammalian alpha-, beta-, and gamma-DNA polymerases.

Antiviral Activity: In Vitro: *In vitro* activity of lamivudine against HBV was assessed in HBV DNA-transfected 2.2.15 cells, HB611 cells, and infected human primary hepatocytes. IC_{50} values (the concentration of drug needed to reduce the level of extracellular HBV DNA by 50%) varied from 0.01 μM (2.3 ng/mL) to 5.6 μM (1.3 μg/mL) depending upon the duration of exposure of cells to lamivudine, the cell model system, and the protocol used. See the EPIVIR package insert for information regarding activity of lamivudine against HIV.

Drug Resistance: HBV: Genotypic analysis of viral isolates obtained from patients who show renewed evidence of replication of HBV while receiving lamivudine suggests that a reduction in sensitivity of HBV to lamivudine is associated with mutations resulting in a methionine to valine or isoleucine substitution in the YMDD motif of the catalytic domain of HBV polymerase (position 552) and a leucine to methionine substitution at position 528. It is not known whether other HBV mutations may be associated with reduced lamivudine susceptibility *in vitro*.

In 4 controlled clinical trials in adults, YMDD-mutant HBV were detected in 81 of 335 patients receiving lamivudine 100 mg once daily for 52 weeks. The prevalence of YMDD mutations was less than 10% in each of these trials for patients studied at 24 weeks and increased to an average of 24% (range in four studies: 16% to 32%) at 52 weeks. In limited data from a long-term follow-up trial in patients who continued

100 mg/day lamivudine after one of these studies, YMDD mutations further increased from 16% at 1 year to 42% at 2 years. In small numbers of patients receiving lamivudine for longer periods, further increases in the appearance of YMDD mutations were observed.

In a controlled trial in pediatric patients, YMDD-mutant HBV were detected in 31 of 166 (19%) patients receiving lamivudine for 52 weeks. For a subgroup who remained on lamivudine therapy in a follow-up study, YMDD mutations increased from 24% at 12 months to 45% (53 of 118) at 18 months of lamivudine treatment.

Mutant viruses were associated with evidence of diminished treatment response at 52 weeks relative to lamivudine-treated patients without evidence of YMDD mutations in both adult and pediatric studies (see PRECAUTIONS). The long-term clinical significance of YMDD-mutant HBV is not known.

HIV: In studies of HIV-1-infected patients who received lamivudine monotherapy or combination therapy with lamivudine plus zidovudine for at least 12 weeks, HIV-1 isolates with reduced *in vitro* susceptibility to lamivudine were detected in most patients (see WARNINGS).

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RECOMMENDATION:

With respect to microbiology, this application is recommended for approval.

_____
Microbiologist

CONCURRENCES:

HFD-530/Dep Dir _____ Signature _____ Date
HFD-530/S micro _____ Signature _____ Date
CC:

HFD-530/Original sNDA (21-003)
HFD-530/ Division File
HFD-530/S Micro
HFD-530/Review Micro
HFD-530/CSO, Lincoln, C.