Table 111. Musculoskeletal Adverse Events within 30 days of CK elevation

Table 4-17 **Summary of on-treatment adverse events possibly related to a myopathic/muscle injury process occurring within ± 30 days of a CK elevation above Baseline – Pooled NV-02B-007/NV-02B-015**

Preferred term	Lamivudine (N=852) n (%)	Telbivudine (N=847) n (%)
Within a new onset of Grade 1/2 CK	330	662
Patients reporting an adverse event	19(4.3)	59(9.9)
Asthenia	2(0.5)	5(0.9)
Fatigue	14(3.2)	35(5.3)
Malaise	1(0.3)	1(0.2)
Muscular weakness	0	1(0.2)
Musculoskeletal discomfort	0	1(0.2)
Myalgia	3(0.8)	12(1.8)
Myopathy	0	2(0.3)
Myositis	1(0.3)	1(0.2)
Pain	0	1(0.2)
Pain in extremity	1(0.3)	6(0.9)
Polymyositis	0	1(0.2)
Within a new onset of Grade 3/4 CK	**34**	**107**
Patients reporting an adverse event	1(2.9)	12(11.2)
Asthenia	0	2(1.9)
Fatigue	1(2.9)	4(3.7)
Malaise	0	0
Muscular weakness	0	0
Musculoskeletal discomfort	0	0
Myalgia	0	5(4.7)
Myopathy	0	0
Myositis	0	0
Pain	0	1(0.9)
Pain in extremity	0	1(0.9)
Polymyositis	0	1(0.9)
Within a new onset of Grade 1-4 CK	**399**	**673**
Patients reporting an adverse event	19(4.8)	65(9.7)
Asthenia	2(0.5)	7(1.0)
Fatigue	14(3.5)	39(5.8)
Malaise	1(0.3)	1(0.1)
Muscular weakness	0	1(0.1)
Musculoskeletal discomfort	0	1(0.1)
Myalgia	3(0.8)	14(2.1)
Myopathy	0	2(0.3)
Myositis	1(0.3)	1(0.1)
Pain	0	1(0.1)
Pain in extremity	1(0.3)	7(1.0)
Polymyositis	0	1(0.1)

Source: Applicant's Table 4-17 summary of clinical safety

Medical Officer's Comments: *In both treatment groups, most patients with CK elevation did not have adverse events associated with muscle injury or myopathy temporally related to the CK elevation. In a subset analysis, the applicant did not find any significant association of these adverse events with race (Asian vs. Caucasian).*

Musculoskeletal Adverse Events in other Studies

One case of myopathy was reported in a patient receiving telbivudine in Study NV-02B-018. This was associated with mild CK elevation (CK 253 IU/L; ULN 195 IU/L), and did not require interruption or discontinuation of telbivudine. This adverse event was ongoing at follow-up and the patient entered the rollover study, NV-02B-022. In that study, which is ongoing, there have

been 3 serious adverse event reports of myopathy or myositis as of the cutoff date of July 31, 2007. Other musculoskeletal adverse events (non-serious) reported by the applicant in study NV-02B-022 were muscular weakness (1), pain in extremity (1), myalgia (3) in patients who entered the study from NV-02B-007. Additionally myositis (Grade 1) was reported in a patient who entered the rollover study from NV-02B-018. The serious musculoskeletal adverse events reported in NV-02B-022 are summarized in the following table. These were also reviewed in Section 7.3.2_above.

Table 112. Serious Adverse Events in Musculoskeletal SOC in Study NV-02B-022 (open-label Telbivudine).

Patient Number	Prior Study Treatment	Adverse Event Preferred Term	Onset After starting LdT	Action	Outcome	CK elevation
022-02B-022	Telbivudine	Myopathy	1 month	Discontinued	Continuing	CK 642 IU/L at baseline
022-032-002	Lamivudine	Toxic myopathy	2 years	Discontinued 2 months prior to onset of AE	Continuing	CK 2910 IU/L at onset of event
022-001-003	Lamivudine	Myopathy Myositis	15 months	Discontinued	Muscle weakness resolved 11 months after AE; myopathy and myositis continuing	CK 282 IU/L 2 months after event

Discontinuation or interruption of Study Drug due to Musculoskeletal Adverse Events

When the adverse event dataset A_AE for the pooled safety database was searched (SOC musculoskeletal and connective tissue disorders) no treatment discontinuations or interruptions were identified in the lamivudine group; however, 4 patients interrupted treatment and 2 discontinued treatment due to musculoskeletal AEs in the telbivudine group, as summarized in the following table.

Table 113.Treatment Discontinuations or Interruptions Due to Musculoskeletal Adverse Events

Action Taken	Lamivudine Number of Patients	Telbivudine Number of Patients	Adverse Event Preferred Terms
Treatment Discontinuation	0	2	Pain in extremity (1) Myopathy (1)
Treatment Interruption	0	4	Myopathy (1), myalgia (2), pain in extremity (1)

Source: SRAS A_AE

In the applicant's analysis, which also included CK elevation and muscle-related adverse events (such as fatigue, asthenia and malaise) as a reason for treatment discontinuation or interruption, 1/852 (0.1%) lamivudine patients discontinued and 1/852 interrupted treatment to CK elevation, or muscle-related adverse events (malaise); while 4/847 (0.4%) telbivudine patients discontinued and 9/847 (1.1%) interrupted treatment due to CK elevation or musculoskeletal adverse events, as summarized in the following table.

Table 114. Discontinuations due to Musculoskeletal AEs or CK Elevation in Major Safety Population

Table 4-19 **Patients who discontinued or interrupted study drug due to elevated creatine kinase, musculoskeletal events, or other selected adverse events – major safety population**

Site-patient ID	Event & grade	SAE	Attribution to study drug	Date of onset	Study day of onset	Date of resolution	Study drug action
Lamivudine							
007-079-004	CK Grade 4	No	Reasonably or possibly	13-May-2005	477	19-May-2005	Discontinued
007-092-016	Malaise Grade 3	Yes	Not reasonably or possibly related	28-Apr-2004	28	03-May-2004	Interrupted
Telbivudine							
007-012-001	CK Grade 2	No	Reasonably or possibly related	20-Jan-2004	280	14-Apr-2004	Interrupted*
	Myopathy Grade 2	Yes	Reasonably or possibly related	09-Feb-2004	300	16-Mar-2005	Interrupted
007-025-008	CK Grade 2	No	Reasonably or possibly related	22-Jul-2004	274	26-Oct-2004	Discontinued
007-054-031	Myopathy Grade 2	No	Reasonably or possibly related	Jan-2005	328	Aug-2006	Discontinued
007-068-021	CK Grade 1	Yes	Not reasonably or possibly related	30-Sep-2004	220	02-Dec-2004	Interrupted
007-071-043	Myalgia Grade 1	No	Reasonably or possibly related	17-Mar-2005	367	30-Mar-2005	Interrupted
007-105-012	Fatigue Grade 2	No	Reasonably or possibly related	01-Oct-2004	260	26-Sep-2005	Interrupted
	Myalgia Grade 2	No	Not reasonably or possibly related	Aug-2004	199	28-Oct-2005	Interrupted
007-119-004	CK Grade 4	No	Not reasonably or possibly related	25-Jan-2006	702	07-Feb-2006	Interrupted

Site-patient ID	Event & grade	SAE	Attribution to study drug	Date of onset	Study day of onset	Date of resolution	Study drug action
007-119-005	Pain in extremity Grade 1	No	Reasonably or possibly related	28-Mar-2005	410	01-Jul-2005	Interrupted
007-122-054	Fatigue Grade 1	No	Reasonably or possibly related	02-Mar-2005	382	28-Jun-2005	Discontinued
007-128-003	CK Grade 1	No	Reasonably or possibly related	02-Sep-2004	172	12-Jul-2005	Interrupted
	CK-MB Grade 1	No	Reasonably or possibly related	05-Mar-2005	355	16-Jul-2005	Interrupted
	CK Grade 4	No	Reasonably or possibly related	26-Dec-2005	651	22-Mar-2006	Interrupted
007-132-002	CK Grade 2	No	Reasonably or possibly related	14-Sep-2005	546	15-Feb-2006	Interrupted
	Asthenia Grade 1	No	Reasonably or possibly related	20-Mar-2005	368	26-Dec-2005	Interrupted
015-008-004	Pain in extremity Grade 1	No	Reasonably or possibly related	14-Jun-2005	308	15-Dec-05	Discontinued
015-007-001	Fatigue Grade 2	No	Not reasonably or possibly related	04-Nov-2005	477	20-Jan-2006	Interrupted
	Hepatic pain Grade 2	No	Not reasonably or possibly related	04-Nov-2005	477	10-Jan-2006	Interrupted

*Patient 007-012-001 had telbivudine discontinued due to treatment efficacy [NV-02B-007 Wk 104 – Listing 16.2.6.6]

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.3.3.1]; [NV-02B-007 Wk 104 – Listing 16.2.7.6] and [NV-02B-015 Wk 104 – Listing 16.2.7.1]

Medical Officer Comments: *Overall more patients interrupted or discontinued telbivudine than lamivudine due to CK elevation, or muscle-related adverse events, including myopathy, myalgia, and pain in extremity, fatigue, asthenia and malaise.*

Peripheral Neuropathy

Peripheral neuropathy has been associated with a number of nucleoside reverse transcriptase inhibitors approved for the treatment of HIV infection, particularly zalcitabine (ddC), didanosine (ddI), and stavudine (d4T). In the original Tyzeka NDA submission, NDA 22-011, only two reports of peripheral neuropathy, described as polyneuropathy were identified in the pivotal clinical study, NV-02B-007 up to week 52. The following table summarizes the treatment-emergent neuropathic or other sensory adverse events reported in the major safety database through 104 weeks.

Table 115. Peripheral Neuropathy and other sensory AEs in Major Safety Population

Table 4-20 **Summary of on-treatment neuropathic or other sensory adverse events – Pooled NV-02B-007/NV-02B-015**

	Lamivudine (N=852)		Telbivudine (N=847)	
Body system/Preferred term	n	(%)	n	(%)
Patients reporting an AE in Nervous System Disorders SOC	22	(2.6)	26	(3.1)
Hypoaesthesia	9	(1.1)	9	(1.1)
Dysgeusia	2	(0.2)	9	(1.1)
Paraesthesia	6	(0.7)	4	(0.5)
Facial palsy	2	(0.2)	0	
Paraesthesia oral	0		2	(0.2)
Polyneuropathy	0		2	(0.2)
Anosmia	0		1	(0.1)
Dysaesthesia	1	(0.1)	0	
Intercostal neuralgia	0		1	(0.1)
Neuralgia	1	(0.1)	0	
Neuropathic pain	0		1	(0.1)
Sciatica	0		1	(0.1)
Sensory loss	0		1	(0.1)
Tremor	1	(0.1)	0	

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.3.5.14]

Medical Officer Comments: *The Adverse Event (SRAS_AE) dataset for studies NV-02B-007 and -015 was searched, and another case of peripheral sensory neuropathy was identified in a patient treated with telbivudine in study NV-02B-007, patient number 007-127-044. Because this patient also experienced a serious adverse event, a narrative summary was provided. This patient was a 53 year-old Maori (New Zealand) male who reportedly had a history of progressive paresthesias in the lower extremities for 10 years prior to study enrollment. He also had a history of postural hypotension. While on study treatment, the patient was hospitalized for acute postural hypotension for which no etiology was found, and was discharged with continued investigation for a progressive peripheral and autonomic neuropathy. After a second hospitalization for postural hypotension, the patient was diagnosed with a pituitary adenoma, diagnosed by a trans-sphenoidal biopsy. Minimal debulking of the tumor was performed, and the patient received radiotherapy. This patient was discontinued from the study early (week 76) by patient request due to multiple health issues. The adverse events of peripheral sensory neuropathy and neuralgia in this patient were not considered treatment-emergent and were not included in the table above. It is agreed that the peripheral neuropathy in this patient was apparently pre-existing, and not likely related to telbivudine.*

Based on the pooled safety data from studies NV-02B-007 and -015, peripheral neuropathy or polyneuropathy were uncommon adverse events with telbivudine treatment in these studies.

Peripheral Neuropathy in Other Studies

No neuropathic or other sensory adverse events were reported in the study report amendment for study report for NV-02B-018 (submitted May 22, 2008), in the study report submitted as an amendment to the efficacy supplement on April 25, 2008, or the original study report submitted

on July 26, 2007. Reports of peripheral neuropathy reported in the applicant's other studies are summarized in the following table.

Table 116. Reports of Peripheral Neuropathy in Recently Completed and Ongoing Studies (from 120-Day Safety Report, 5/30/08)

Peripheral Neuropathy	Study NV-02B-019	Study NV-02B-004	Study CLDT600A2406*	Study NV-02B-011/CLDT600A2301	Study NV-02B-022/CLDT600A2303
Number of AE Reports	0	3-LdT 1-LdT+LdC	1-LdT 7-LdT+Pegasys	6 (blinded)	3-LdT

*Combination treatment arm stopped January 8, 2008 due to increased risk of peripheral neuropathy in the LdT plus Pegasys combination arm. Study stopped May 15, 2008 because study objectives could not be met.

Medical Officer Comments: *For study CLDT600A2406, the incidence of peripheral neuropathy cases was updated by the applicant at the Division's request on August 26, 2008. In the applicant's email response of August 28, 2008, 1/53 (1.9%) cases of peripheral neuropathy with telbivudine alone, 11/48 (23%) cases with telbivudine plus Pegasys, and 0/54 cases with Pegasys alone were reported in this study. These preliminary data would suggest that the risk for peripheral neuropathy is increased significantly with concurrent telbivudine and Pegasys, and although peripheral neuropathy has been reported with interferons, it has been considered a rare event. The potential mechanism for this possible pharmacodynamic interaction is currently unknown.*

In study NV-02B-004, 3 cases of "peripheral neuropathy" were reported in the LdT treatment arm. These cases were reported as "hypoesthesia" (2); and facial palsy (1). No further information was provided. In the ongoing Study 011/CLDT600A2301 which is evaluating telbivudine vs. lamivudine for treatment of chronic hepatitis B in patients with decompensated liver disease, a total of 6 patients experienced symptoms of peripheral neuropathy but the treatment arms remain blinded at this time. These events are further described in the following table.

Table 117. Peripheral Neuropathy in Study 011

Table 3-3 Listing of patients in NV-02B-011/ CLDT600A2301 who reported peripheral neuropathy events (safety population)

Pt ID	Preferred Term	Study day at onset	Severity (SAE tox grade)	Relationship to study drug	Outcome
24-6	Paraesthesia	272	1	Not related	Continuing
24-16	Sensory disturbance	73	1	Not related	Resolved (no residual effect)
83-8	Paraesthesia	467	1	Not related	Continuing (no residual effect)
85-7	Peripheral sensory neuropathy	290	1	Not related	Resolved (no residual effect)
91-3	Paraesthesia	189	1	Not related	Resolved (no residual effect)
91-8	Paraesthesia	17	1	Not related	Resolved (no residual effect)

Source: NV-02B-011/ CLDT600A2301 Listing 1-2 and Table 6-2

In study NV-02B-022, descriptive information on 2 of the 3 reported cases of peripheral neuropathy was provided in the 120-Day Safety Update. In both cases, patients reportedly had a history of neuropathy or progressive lower limb weakness prior to enrollment in the 022 study; however, to be enrolled in that study patients would have received prior treatment with telbivudine or comparator, so they may have received telbivudine previously.

The following table provides a description of the peripheral neuropathy cases from Studies NV-02B-022 and CLDT600A2406 from brief narratives provided by the applicant in the 120-Day Safety Update.

Table 118. Description of Peripheral Neuropathy Cases in recently completed or ongoing studies (From 120-day safety report of 5/30/08)

Patient ID Study Number	Age and gender	Study Drug(s)	Adverse Event(s)	Serious AE?	Onset of AE	Action	Outcome
MCN PHH02007US11998 NV-02B-022	54 M	LdT	Sensory neuropathy (by EMG) initially reported as necrotizing myopathy with increasing muscle weakness	NR	Muscle weakness started about 20 months after starting LdT; 2-year history of prior neuropathy; peripheral neuropathy reported at 638 days	Self-discontinued treatment	Ongoing
MCN PHH02007SG1299 NV-02B-022	64 unknown gender	LdT	Muscle weakness in LE (diagnosed as proximal myositis); elevated CK;	NR	Muscle weakness started approximately 1.5 years after starting LdT; but	Not reported	Not reported

			NCS mild to mod. Axonal peripheral neuropathy; MRI degenerative disc disease L1/L2 and L2/3		had history of progressive LE weakness for 1 year; peripheral neuropathy reported at 618 days		
MCN PHH2007IL18914 CLDT600A2406	23 female	LdT	Paresthesia and dysesthesia of LE in "sock" distribution EMG confirmed sensory axonal polyneuropathy (small and large fibers)	Yes	115 days	Temporarily interrupted	Improved, but ongoing
MCN PHHO2007IL15386 CLDT600A2406	21 M	LdT +Pegasys	Weakness and paresthesias both LEs; decreased sensation distal hands and feet (suspected polyneuropathy); EMG and NCS confirmed sensory motor polyneuropathy	Yes	67 days	Hospitalized; study meds discontinued; no treatment for AE	Improved
MCN PHHO2007IL15885 CLDT600A2406	24 F	LdT + Pegasys	Bilateral leg pain; Peripheral sensory neuropathy – bilateral (EMG confirmed)	Yes	128 days	Study medication discontinued	Improved with amytriptyline
MCN PHHO2007SG20555 CLDT600A2406	45 M	LdT + Pegasys	Numbness in legs; NCS showed generalized axonal polyneuropathy in LEs	Yes	89 days	Study medications discontinued	Stable-ongoing (note that this pt. was also found to have vitamin B12 deficiency)
A2406/103-007 CLDT600A2406	59 M	LdT + Pegasys	Myalgia; paresthesia LEs Presumptive diagnosis of myopathy and distal symmetric polyneuropathy by neurologist	No	3 months	Study medication discontinued; treated with Pregabalene	Ongoing-unchanged
MCN **PHHOAR20971/** A2406-103-002 CLDT600A2406	47 M	LdT + Pegasys	Myositis/myalgia; elevated CK; then mild paresthesia LE initially (and EMG normal), then worsened	Yes	Myositis/myalgia and elevated CK; Peripheral neuropathy-approximately 2-3 months	Study medications discontinued	Peripheral neuropathy-improving, but "still significant disability"

			EMG showed incipient mild polyneuropathy LEs				Myalgia-improved CK elevation -resolved
MCN PHHO2008TW00556 CLDT600A2406	27 M	LdT + Pegasys	Bilateral foot numbness; EMG diagnosis was bilateral L5/S1 radiculopathy	Yes	92 days	Not reported	ongoing
MCN PHHO2008AR01016 CLDT600A2406	55 M	LdT + Pegasys	Hyperalgesia and paresthesia both legs; peripheral neuropathy diagnosed by neurologist; EMG: demyelinating motor and sensory polyneuropathy	Yes	168 days	Study medications discontinued	Improved
MCN PHHO2008NZ00755 CLDT600A2406	32 M	LdT + Pegasys	Paresthesia both feet with pain and clumsiness with walking; diagnosed as peripheral sensory neuropathy (axonal); confirmed by NCS	Yes	186 days	Study medications discontinued	unknown

NR= not reported
Note that those MCN's that are bolded were also identified in the AERS database, and are also reviewed as postmarketing adverse event reports, below.

Medical Officer Comments: *A total of 9 cases of peripheral neuropathy in study CLDT600A2406 are described in the table above, 8 of these were considered SAEs. One case was reported in a patient on telbivudine monotherapy; while 8 reports were in patients who received combination pegylated interferon plus telbivudine. In that study, the onset of symptoms consistent with peripheral neuropathy ranged from approximately 3 to 6 months. In many of the cases in which study medication were discontinued, symptoms of peripheral neuropathy had not resolved at the time of follow-up by the sponsor. Additional information was requested from the applicant (September 5, 2008) regarding the cases of peripheral neuropathy in that study reported after the submission of the safety update, including the outcome of the adverse events, and the duration of follow-up in these patients. At this time, insufficient information is available to determine the reversibility of peripheral neuropathy after drug discontinuation.*

The applicant has estimated the incidence of peripheral neuropathy as 23% when telbivudine was used in combination with pegylated interferon (pegasys), and 1.9% with telbivudine alone, based on the preliminary safety results from study CLDT600A2406. In contrast, in the large phase 3 registrational trial (NV-02B-007), 2/680 (0.3%) LdT-treated patients experienced

peripheral neuropathy (described as polyneuropathy) while on-treatment, and in the pooled major safety data from studies NV-02B-007 and -015, only 2 cases of treatment-emergent polyneuropathy were reported. Additional cases of peripheral neuropathy with telbivudine alone have been reported in recently completed and ongoing trials, but there is currently insufficient information to calculate an incidence of peripheral neuropathy with telbivudine alone.

In study 022, descriptive information on 2 of the 3 reported cases of peripheral neuropathy was provided in the safety update. In both cases, patients reportedly had a history of neuropathy or progressive lower limb weakness prior to enrollment in the 022 study; however, to be enrolled in that study patients would have received prior treatment with telbivudine or comparator, so they may have received telbivudine previously. In study 004, 3 cases of "peripheral neuropathy" were reported in the telbivudine treatment arm. These cases were reported as "hypoesthesia" (2); and facial palsy (1). No further information was provided in the 120-Day Safety Update; but some additional information was submitted September 22, 2008 in response to an FDA request, and is reviewed below.

In the applicant's response of September 22, 2008 to the Division's request for additional information regarding the cases of peripheral neuropathy reported in study CLDT600A2406, three additional serious cases of peripheral neuropathy in study CLDT600A2406 were reported, bringing the total number to 11 for serious AE cases of peripheral neuropathy in that study. In the applicant's search of their ARGUS safety database using the standard MedDRA query (SMQ) for peripheral neuropathy, a total of 38 adverse reactions with at least one synonym from the SMQ for peripheral neuropathy were identified, including the 11 SAEs from CLDT600A2406, and 11 non-serious cases from the clinical database, 8 in patients on combination therapy (telbivudine plus pegylated interferon-alfa-2a) and 3 in patients who received pegylated interferon-alfa-2a alone. Among the 38 cases identified in the ARGUS database, 18 had other associated diagnoses (e.g. radiculopathy due to disc prolapse, cerebellar infarction, etc.) and were not further described in the September 22, 2008 submission. The other twenty cases (19 SAEs and 1 non-serious case) were further described in the submission.

For patients from study CLDT600A2406, the new information provided regarding the onset of peripheral neuropathy symptoms, and outcome at last follow-up was incorporated into Table 118 above. New information regarding 3 additional cases from that study is provided in the following table.

Table 119. New cases of Peripheral Neuropathy in Study CLDT600A2406

Patient ID Study Number	Age and gender	Study Drug(s)	Adverse Event(s)	Serious AE?	Onset of AE	Action	Outcome
PHHO2008TW03720	33/male	LdT + Pegasys	Muscle pain and numbness over big toes bilaterally; NCS showed polyneuropathy with predominant sensory-motor axonal degeneration; also bilateral carpal tunnel syndrome	NR	4 months	LdT stopped	ongoing
PHHO2008GB04149	24/female	LdT + Pegasys	Peripheral neuropathy both toes; EMG showed mild sensory peripheral neuropathy	NR	3 months	LdT and Pegasys discontinued; tenofovir started	Worsenin symptoms "still causing significant disability and inability t work"
PHHO2008SG07712	40/male	LdT	Numbness right arm; numbness left arm and soles of feet; NCS did not confirm PN (diagnosed with radiculopathy)	NR	1 month	No treatment interruption	Ongoing

Source: Applicant's response of September 22, 2008 to FDA request

Medical Officer Comment: *Based on the new safety signal of peripheral neuropathy in study CLDT600A2406, the applicant updated the Core Data Sheet for telbivudine and issued a Dear Healthcare Professional letter in February, 2008.*

In the September 22, 2008 submission, the applicant also provided information on patients with non-serious adverse events consistent with symptoms of peripheral neuropathy in Study CLDT600A2406 from their ARGUS safety database. As of August 31, 2008, 11 non-serious

AEs were identified in the clinical database, 11 in the telbivudine-pegylated interferon-alfa-2a combination arm, and 3 in the pegylated interferon-alfa-2a monotherapy arm, as shown in the following table.

Table 120. Listing of Patients in Study CLDT600A2406 with Non-Serious AEs in peripheral neuropathy SMQ search of ARGUS database

PT ID	Preferred Term	Time to onset in days	Relationship to study drug	Outcome at last follow up
Telbivudine and pegylated interferon alfa-2a				
0154-00005	Polyneuropathy	6 months172	suspected	ongoing
0102-00002	Stocking paresthesia	136	suspected	ongoing
0101-00007	Paresthesia Peripheral neuropathy	93	suspected	ongoing
0206-00006	Peripheral neuropathy Worsening of polyneuropathy	77 (worsening on 146)	suspected	ongoing
0165-00006	Tingling in right arm	51	suspected	ongoing
0183-00002	Numbness both soles	301	not provided	ongoing
0177-00006	Numbness over both lower feet	211	not suspected	ongoing
0103-007	Polyneuropathy distally symmetric	unknown	unknown	ongoing
Pegasys monotherapy				
0148-00006	Hand paresthesia	70	suspected	ongoing
0170-00008	Muscle weakness	32	suspected	ongoing
0170-00006	Tingling in both hands	127	not suspected	ongoing
Telbivudine monotherapy				
No cases reported				
Source: Clinical trial database				

Source: Applicant's submission of September 22, 2008

Medical Officer Comments: *The adverse events reported above are all consistent with peripheral neuropathy. No non-serious AEs in the peripheral neuropathy SMQ search were reported in the telbivudine monotherapy arm of the study.*

In response to the Division's question regarding the reversibility of peripheral neuropathy experienced by patients in Study CLDT600A2406, the applicant noted that in patients treated with the telbivudine-pegylated interferon-alfa-2a combination, time to onset of peripheral neuropathy symptoms ranged from 2 to 6 months in comparison to patients who experienced peripheral neuropathy on telbivudine alone, in whom time to onset was much longer. Additionally, peripheral neuropathy adverse events in the combination therapy group required treatment discontinuation and were frequently considered serious adverse events. Among patients who experienced peripheral neuropathy in this study, improvement has been noted in 5 of the 11 serious cases.

The applicant also searched the clinical trials database, including 2200 patients treated with telbivudine in clinical trials using the peripheral neuropathy SMQ to identify additional cases from studies other than Study CLDT600A2406. These are summarized in the following table.

Table 121. Cases of Peripheral Neuropathy from Other Clinical Trials identified using SMQ for peripheral neuropathy

Subject ID and Study	Age and gender	Study Drug(s)	Adverse Event(s)	Serious AE?	Onset of AE	Action	Outcome	MO Assessment
PHH02006HK18502 Study NV-02B-004	31/male	LdT	RUE numbness, dizziness; NCS: mild axonal degeneration of right median sensory nerve	Yes	9 months	Treatment interrupted one day and then continued	Complete resolution in 4 months	Consistent with carpal tunnel syndrome; unlikely related
PHHO2006NZ11169	28/male	LdT	Acute onset of paraesthesia secondary to cervical disc protrusion	Yes	4 months	Treated surgically with C3-C6 laminoplasty	Complete resolution in 3 months	Symptoms most likely secondary to disc protrusion in patient with history of prolapsed disc in neck
PHHO2007SG20555 NV-02B-022	45/male	LdT	Peripheral neuropathy (muscle weakness in legs: NCS: mild to moderate axonal peripheral neuropathy	Yes	19 months	Discontinued LdT	Full recovery in 9 months	Probably related
PHHO2007US11998 NV-02B-022	54/male	LdT	EMG: sensory disturbance consistent with sensory neuropathy; Muscle biopsy: necrotizing myopathy; CK elevations	Yes	15 months	LdT discontinued	Improved (15 month follow-up so far)	Probably related
PHHO2008IL04948 NV-02B-022	63/male	LdT	Mild diffuse sensory neuropathy with paresthesia	Yes	21 months	NR	unknown	Unable to assess

			and numbness, multi-focal and symmetric					
PHHO2008IL07965 NV-02B-022	68/female	LdT	Polyneuropathy (numbness in lower limbs, distal and symmetric); EMG: sensory polyneuropathy	Yes	20 months	LdT discontinued	Unchanged (3 month follow-up so far)	Probably related
PHHO2008NZ05947 NV-02B-022	45/female	LdT	Weakness of hip girdle; EMG: generalized myopathy LEs and thoracic paraspinals with evidence of reinervation of left tibialis anterior and vastus medialus, but no evidence for generalized polyneuropathy	Yes	25 months	LdT discontinued	Unchanged (4 month follow-up so far)	This AE could be classified as myopathy rather than peripheral neuropathy; probably related
PHHO2008TW02549 NV-02B-022	56/male	LdT	Muscle weakness, sensory motor neuropathy; elevated CK: EMG: mild sensory-motor polyneuropathy with predominant demyelination; muscle biopsy confirmed inflammatory myopathy c/w polymyositis	Yes	16 months	LdT discontinued	Improved (4 months follow-up so far)	Possible co-existent myopathy and peripheral neuropathy; probably related
PHHO2007TW18284 NV-02B-011	52/male	Blinded treatment	Weakness in upper extremities and back; EMG: possible peroneal neuropathy,	No	10 months	Treatment interrupted for one week; and then restarted	Recovered (7 months follow-up so far)	Possibly related

			multifocal, symmetric, proximal; elevated CK					

Source: September 22, 2008 submission by applicant in response to FDA request
NR= not reported

The applicant also summarized peripheral neuropathy adverse events in the completed phase 2 or 3 trials. No serious adverse events of peripheral neuropathy (or symptoms, thereof) were reported in studies 007 or 015. Non-serious adverse events of peripheral neuropathy or symptoms associated with peripheral neuropathy are summarized in the following table. No peripheral neuropathy adverse events were identified in Studies NV-02B-010, NV-02B-018, NV-02B-019, CLDT600A2407, or CLDT600A2304.

Table 122. Peripheral Neuropathy as Non-Serious Adverse Event in Completed Phase 3 Clinical Studies

Patient ID Study	Age and gender	Study Drug(s)	Adverse Event(s)	Onset of AE	Action	Outcome
008-004 NV-02B-007	48/male	LdT	Polyneuropathy	13 months	none	Ongoing at end of 007 study; but patient rolled over into 022 study and completed 2 years LdT treatment
073-001 NV-02B-007	62/female	LdT	Polyneuropathy	15 months	none	Continuing at end of study 007; Improved (3 month follow-up)
004-009 NV-02B-015	26/male	LdT	Oral hypoaesthesia; Hypogeusia	3 months; 12 months	None None	Recovered (9 month follow-up; Ongoing (12 month follow-up)
007-018 NV-02B-015	37/male	LdT	Hypoesthesia	9 months	None	Recovered (4.5 month follow-up)

018/00017 NV-02B-015	33/male	LdT	Dysgeusia Hypoesthesia	3 months 10 months	None None	Recovered (3 month follow-up) Recovered (7 month follow-up)

Source: Applicant's September 22, 2008 submission (via email) in response to FDA request: additional information obtained from AE datasets for studies 007 and 015
See Section 5.3 for review of neuropathic AEs in the 007 and 015 studies.

Medical Officer Comments: *It is not clear whether the terms, oral hypoesthesia (verbatim term, numbness of tongue), hypogeusia, and dysgeusia (bitter taste) should be included with peripheral neuropathy adverse events.*

The applicant concluded the following from this additional analysis of peripheral neuropathy events which occurred in the telbivudine clinical studies:

- An increased risk of peripheral neuropathy was observed with the combination of telbivudine plus pegylated interferon-alfa-2a in study CLDT600A2406.

- In CLDT600A2406, the clinical features of peripheral neuropathy in the telbivudine/pegylated interferon treatment arm differed from that observed in patients treated with telbivudine monotherapy with respect to onset, severity, and reversibility. Onset of these events in the telbivudine combination arm appeared to be more rapid, severity was greater, and serious adverse events predominated in comparison to patients receiving telbivudine monotherapy. At this time, the reversibility of peripheral neuropathy in the combination treatment arm appears limited, possibly due to short length of follow-up.

- In the clinical development program for telbivudine, peripheral neuropathy was uncommon, reported (as polyneuropathy) in 2/680 (0.3%) patients. Clinical features of peripheral neuropathy (or symptoms associated with peripheral neuropathy) differ from those observed with the telbivudine/pegylated interferon combination with respect to onset (late onset with telbivudine monotherapy), shorter duration, recovery without treatment interruption, and predominance of non-serious events.

Medical Officer Comments: *This reviewer agrees with the applicant's assessment of peripheral neuropathy events reported in the clinical studies of telbivudine.*

ALT Flares

The AASLD definition of hepatitis flares or ALT flares, ALT > 10 x ULN and > 2 x baseline ALT (Lok and McMahaon, 2007) was used to identify patients with acute exacerbations of hepatitis while on-treatment or post-treatment in the major safety population. Hepatitis flares may be due to development of antiviral resistance, or due to rapid outgrowth of wild-type virus after treatment discontinuation, in patients co-infected with HIV and low CD4 counts who experience immune reconstitution after initiation of HAART, or with HBeAg seroconversion. Particularly in patients with cirrhosis, hepatitis flares may be associated with hepatic decompensation. The following table shows the incidence of ALT flares by treatment group in the pooled major safety population by 6 month intervals. The overall incidence of ALT flares was higher in patients treated with lamivudine than with telbivudine, mostly due to ALT flares after week 24; while the incidence from baseline to week 24 was similar in each group.

Table 123. ALT Flares in Major Safety Population

Table 5-5 Summary of ALT (IU/L) flare using AASLD definition by 6-month intervals – Pooled NV-02B-007/NV-02B-015

ALT Flare	Lamivudine (N=852) n (%)	Telbivudine (N=847) n (%)
Overall	67/852 (7.9)	41/847 (4.8)
Baseline to Week 24	25/852 (2.9)	25/847 (3.0)
Week 24 to Week 52	14/837 (1.7)	3/834 (0.4)
Week 52 to Week 76	16/807 (2.0)	6/812 (0.7)
Week 76 to Week 104	15/753 (2.0)	10/774 (1.3)
Week 104 to End of Study	1/54 (1.9)	0
Week 24 to End of Study	44/837 (5.3)	17/834 (2.0)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.4.2.1]

The applicant also performed a logistic regression analysis to determine factors associated with ALT toxicity grade 3 or 4 in the pooled major safety population. Lower baseline ALT and presence of cirrhosis were associated with a higher risk of ALT toxicity Grade 3 or 4 (odds ratios of 5.6 for baseline ALT in tertile 1 vs. tertile 3 and 1.93 for presence of cirrhosis; while treatment with telbivudine resulted in a lower risk (odds ratio 0.46) in this analysis. A lower baseline HBV DNA also resulted in a lower risk (odds ratio 0.27 for tertile 1 vs. tertile 3).

Table 124. Post-Treatment ALT Flares in Major Safety Population

Table 5-7 Summary of post-treatment ALT (IU/L) flares using AASLD definition – Pooled NV-02B-007/NV-02B-015

ALT Flare	Lamivudine (N=180) n (%)	Telbivudine (N=154) n (%)
ALT elevation > 2x Baseline and > 10x ULN	10/180 (5.6)	9/154 (5.8)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.4.2.4]

Medical Officer Comments: *The above table represents those patients who discontinued treatment prematurely or completed Study 007/015 and were not rolled over into study 022. These patients were followed monthly for 4 months post-treatment.*

Other Class Effects of Nucleoside Analogues

In the pooled major safety database for studies NV-02B-007 and -015, there were no cases of lactic acidosis identified. However, two cases were identified in the AERS database for telbivudine.

Medical Officer Comments: *Lactic acidosis and severe hepatomegaly with hepatic steatosis are included in the class Warning for nucleosides, including in the current TYZEKA label, where it is a BOXEDWARNING.*

There was 1 case of pancreatitis reported as an adverse event in the pooled major safety database. This was reported in a 57-year old Caucasian male who received telbivudine in study NV-02B-007. The pancreatitis was considered mild and self-limited, of Grade 1 toxicity, and was not a serious adverse event. Laboratory data for this patient was reviewed, and the maximum amylase level was 149 U/L at the week 68 visit (normal range 20-112 U/L), and baseline amylase was within normal limits. The maximum lipase elevation in this patient was to 177 U/L (normal 0-60 U/L); and baseline lipase was normal (60 U/L).

See also Section 7.7 for review of postmarketing adverse events of pancreatitis and lactic acidosis.

Medical Officer Comments: *Based on the clinical studies with telbivudine and the limited postmarketing data available at this time, pancreatitis does not appear to be a major safety concern with telbivudine to date.*

7.3.5 Submission Specific Primary Safety Concerns

For NDA 22-011 S-001, 104 week safety data for telbivudine was evaluated from the pivotal study, NV-02B-007 and the supportive study, NV-02B-015. Please refer to Sections 5.3 and 7.3 for analysis of 104 week safety of telbivudine. Previously identified safety concerns with telbivudine included CK elevation, myopathy, ALT flares, lactic acidosis and hepatic steatosis. In the review of the 104 week safety data from the clinical studies, no new safety signals were identified.

However, a new safety concern was identified from the postmarketing adverse event data, including data from a clinical study (CLDT600A2406), which was recently stopped prematurely due to development of peripheral neuropathy. In that study, peripheral neuropathy occurred more frequently, was more rapid in onset, and may have been more severe in patients receiving telbivudine plus pegylated interferon-alfa-2a in comparison to telbivudine monotherapy. In the pivotal clinical study, 007, peripheral neuropathy (polyneuropathy) was reported in 2/680 (0.3%) patients treated with telbivudine. See section 7.7 for further review of peripheral neuropathy with telbivudine.

Lactic acidosis and severe hepatomegaly with hepatic steatosis are considered nucleoside/tide-related adverse events. None of these adverse events were reported in the pivotal study, 007, or the supportive study, 015 with telbivudine. However, postmarketing reports of lactic acidosis and hepatic steatosis with telbivudine are reviewed in section 7.7 No additional new safety concerns were identified with review of NDA 22-011 S-001 or NDA 22-154.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events in the pooled studies 007 and 015 are shown in the following table.

Table 125. Common Adverse Events (> 2% Patients) in Major Safety Population

Table 4-6 On-treatment adverse events by decreasing frequency for events occurring in more than 2% of patients on telbivudine – Pooled NV-02B-007/NV-02B-015

	Lamivudine (N=852)		Telbivudine (N=847)	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients reporting an adverse event	630	(73.9)	659	(77.8)
Nasopharyngitis	136	(16.0)	163	(19.2)
Upper respiratory tract infection	122	(14.3)	129	(15.2)
Fatigue	95	(11.2)	106	(12.5)
Blood creatine phosphokinase increased	52	(6.1)	90	(10.6)
Headache	95	(11.2)	83	(9.8)
Cough	45	(5.3)	52	(6.1)
Diarrhoea	46	(5.4)	50	(5.9)
Abdominal pain upper	52	(6.1)	49	(5.8)
Post procedural pain	45	(5.3)	49	(5.8)
Influenza	56	(6.6)	46	(5.4)
Nausea	40	(4.7)	45	(5.3)
Pharyngolaryngeal pain	31	(3.6)	38	(4.5)
Arthralgia	38	(4.5)	37	(4.4)
Pyrexia	27	(3.2)	34	(4.0)
Back pain	32	(3.8)	33	(3.9)
Rash	21	(2.5)	33	(3.9)
Dizziness	43	(5.0)	32	(3.8)
Abdominal pain	31	(3.6)	29	(3.4)
Alanine aminotransferase increased	31	(3.6)	27	(3.2)
Myalgia	17	(2.0)	27	(3.2)
Dyspepsia	39	(4.6)	24	(2.8)
Insomnia	22	(2.6)	24	(2.8)
Abdominal distension	19	(2.2)	22	(2.6)
Hypertension	15	(1.8)	20	(2.4)
Asthenia	11	(1.3)	19	(2.2)
Pruritus	23	(2.7)	18	(2.1)
Toothache	16	(1.9)	18	(2.1)
Gastritis	13	(1.5)	17	(2.0)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.3.1.6]

Medical Officer Comments: *Those adverse events more common in telbivudine arm were nasopharyngitis, upper respiratory tract infection, fatigue, increased CK, cough, diarrhea, post-procedural pain, nausea, pharyngolaryngeal pain, pyrexia, rash, myalgia, insomnia, abdominal distension, hypertension, asthenia, toothache, and gastritis.*

The following table shows a summary of adverse events in the pooled safety database in the reviewer's analysis. The A_AE dataset for pooled studies 007 and 015 were searched first for SOC, and then within each SOC, preferred terms were enumerated. The SOCs and PTs shown in

this table include those which were common events, those reactions in which there appeared to be an imbalance between treatment groups, and those events previously identified as significant with respect to the known safety profile of telbivudine. Note that in this table the numbers of adverse events are shown for the preferred term; while number of events and number of patients is shown for SOC. Thus an adverse event could be reported more than once for an individual patient, and incidence for each preferred term was not calculated. Note also that some preferred terms were pooled with similar terms to obtain a clearer picture of frequency for similar events which were coded differently.

Table 126. Number of Adverse Events in Pooled Safety Database by SOC and select PT

Adverse Events SOC and PT	Lamivudine N= Number of events (number of patients)	Telbivudine N= Number of events (number of patients)
Blood and Lymphatic System Disorders:	11 (6)	14 (13)
Anemia	3	2
Neutropenia	**5**	1
Thrombocytopenia	1	2
Cardiac disorders:	17 (15)	21 (17)
Arrhythmia	1	4
Bradycardia or sinus bradycardia	1	1
Sinus tachycardia or tachycardia	2	0
Atrial fibrillation	0	1
Gastrointestinal Disorders:	466 (265)	498 (273)
Abdominal pain, [a]	126	127
Abdominal distension	22	**26**
Dyspepsia	**46**	26
Gastritis [b]	17	**23**
GERD	10	12
Nausea	45	**52**
Vomiting	22	**27**
Diarrhea	50	**57**
Toothache	19	19
Pancreatitis	0	1
General Disorders and Administration Site	238 (173)	273 (187)
Fatigue	121	**129**
Asthenia	12	**24**
Pyrexia	30	**38**
Malaise	7	4
Lethargy	**13**	7

Influenza-like illness	19	**25**
Immune System Disorders:	12 (11)	7 (5)
Hypersensitivity or drug hypersensitivity	2	1
Infections and Infestations:	707 (382)	771 (394)
Hepatitis B	**36**	17
Investigations:	233 (114)	254 (142)
Blood CK increased	77	**124**
ALT increased	**39**	28
AST increased	**18**	9
Blood amylase increased	**32**	16
lipase increased	**23**	15
Blood bilirubin increased	**5**	1
Metabolism and Nutrition Disorders:	28 (26)	42 (37)
Anorexia or decreased appetite	17	**28**
Musculoskeletal and connective tissue disorders:	198 (127)	192 (137)
Arthralgia	**50**	45
Back pain	**45**	38
Myalgia	18	**33**
Neck pain	8	**11**
Pain in extremity	12	**15**
Myopathy	0	2
Myositis	1	2
Polymyositis	0	2
Neoplasms benign, malignant, and unspecified	12 (11)	13 (11)
Hepatic neoplasms [c]	**4**	2
Nervous System Disorders:	243 (154)	197 (141)
Dizziness	**55**	40
Headache d	**145**	102
Peripheral neuropathy [e]	10	**23**
Dysgeusia	3	**10**
Renal and urinary disorders	19 (16)	30 (24)
Calculus, urinary [f]	1	**9**
Chromaturia	**4**	1
Hematuria	3	2

Respiratory, thoracic and mediastinal disorders:	203 (128)	194 (132)
Cough	59	**63**
Pharyngolaryngeal pain [g]	47	**54**
Skin and subcutaneous tissue disorders:	149 (116)	144 (110)
Pruritus	**28**	20
Rash [h]	44	**50**
Toxic skin eruption	1	0
Urticaria	6	**9**
Facial swelling or edema	1	2

n= number of adverse events
[a] includes abdominal discomfort, abdominal pain, abdominal pain (upper or lower), abdominal tenderness, epigastric discomfort
[b] includes gastritis, erosive gastritis, and hemorrhagic gastritis
[c] includes hepatic neoplasm, and malignant hepatic neoplasm
[d] includes headache and migraine, sinus headache, tension headache
[e] includes peripheral sensory neuropathy, polyneuropathy, dysaesthesia, paraesthesia, hypoaesthesia, sensory loss, neuropathic pain, neuralgia
[f] includes calculus, urinary, calculus, ureteric, nephrolithiasis
[g] includes cough and productive cough
[h] includes rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, pruritic rash, scaly rash, erythema

Adverse events reported more frequently (difference in number of events ≥ 3) in the telbivudine group included arrhythmia, abdominal distension, gastritis, nausea, vomiting, diarrhea, fatigue, asthenia, pyrexia, influenza-like illness, blood CK increased, anorexia, myalgia, neck pain, pain in extremity, peripheral neuropathy, dysgeusia, urinary calculus, cough, pharyngolaryngeal pain, rash, and urticaria. Note that no other descriptors were found for the preferred term arrhythmia, and if bradycardia and tachycardia were included in the term arrhythmia, the total number of adverse events for "arrhythmia" is similar in both treatment groups (lamivudine, 4; telbivudine 6). None of the arrhythmia events in either treatment group were considered serious AEs except for the atrial fibrillation in one patient.

Adverse events reported more frequently (difference in number of events ≥ 3) in the lamivudine group were neutropenia, dyspepsia, lethargy, hepatitis B, increased ALT, increased AST, increased amylase, increased lipase, increased bilirubin, arthralgia, back pain, dizziness, headache, chromaturia, and pruritus.

Medical Officer Comments: *The occurrence of the first adverse event in a patient may predispose to recurrence of that event in the same patient. Thus, this analysis by number of adverse events may not be as useful as an analysis by number of patients, as shown in Table 125 above. .*

Less Common Adverse Events

See Section 5.3 Individual Studies

Adverse Event Severity

Selected on-treatment adverse events of Grade 2 to 4 severity in the pooled major safety database (007 and 015) are shown in the following table. The proportion of patients with moderate to severe adverse events was similar in both treatment arms.

Table 127. Selected Grade2 -4 Adverse Events in Major Study Population

Table 4-10 Selected treatment-emergent clinical adverse events (Grade 2-4) of moderate to severe intensity – Pooled NV-02-007/NV-02B-015

	Lamivudine (N=852)		Telbivudine (N=847)	
SOC/Preferred term	**n**	**(%)**	**n**	**(%)**
Patients reporting any Grade 2-4 adverse event	229	(26.9)	239	(28.2)
General				
Fatigue/Malaise[1]	12	(1.4)	12	(1.4)
Pyrexia	5	(0.6)	9	(1.1)
Musculoskeletal & connective tissue				
Arthralgia	9	(1.1)	8	(0.9)
Muscle-related symptoms[2]	14	(1.6)	15	(1.8)
Gastrointestinal				
Abdominal pain[3]	5	(0.6)	9	(1.1)
Diarrhea/loose stool[4]	6	(0.7)	6	(0.7)
Gastritis	4	(0.5)	7	(0.8)
Respiratory, thoracic, & mediastinal				
Cough[5]	5	(0.6)	5	(0.6)
Nervous system				
Headache[6]	17	(2.0)	10	(1.2)

[1] Includes preferred terms: fatigue and malaise.
[2] Includes preferred terms: back pain, fibromyalgia, muscle cramp, musculoskeletal chest pain, myalgia, myopathy, pain, pain in extremity, tenderness, muscular weakness, musculoskeletal discomfort, musculoskeletal pain, myositis, polymyositis.
[3] Includes preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain.
[4] Includes preferred terms: diarrhoea, loose stools and frequent bowel movements.
[5] Includes preferred terms: cough and productive cough.
[6] Includes preferred terms: headache, migraine, sinus headache, tension headache.
Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.3.4.4]

Medical Officer Comments: *For these selected moderate to severe adverse events, no major differences were observed between treatment groups.*

Drug-Related Adverse Events

In the pooled major safety population, a higher proportion of telbivudine recipients experienced adverse events considered at least possibly related to study medication by the investigator. Drug-related adverse events that were reported more frequently in patients receiving telbivudine than lamivudine included increased CK, nausea, diarrhea, fatigue, dizziness, and rash.

Table 128. Drug-Related Adverse Events (> 1%) in the Major Safety Population

Table 4-11 Study drug-attributed adverse events in more than 1% of patients in either treatment arm – Pooled NV-02B-007/NV-02B-015

	Lamivudine (N=852)		Telbivudine (N=847)	
Body system/Preferred term	n	(%)	n	(%)
Patients reporting a drug-attributed adverse event	171	(20.1)	218	(25.7)
Investigations	57	(6.7)	86	(10.2)
Blood creatine phosphokinase increased	29	(3.4)	69	(8.8)
Alanine aminotransferase increased	17	(2.0)	17	(2.0)
Lipase increased	10	(1.2)	11	(1.3)
Blood amylase increased	9	(0.9)	10	(1.2)
Aspartate aminotransferase increased	9	(1.1)	7	(0.8)
Gastrointestinal disorders	59	(6.9)	65	(7.7)
Nausea	17	(2.0)	22	(2.6)
Diarrhoea	6	(0.7)	11	(1.3)
Abdominal pain upper	11	(1.3)	6	(0.7)
General disorders and administration site conditions	34	(4.0)	60	(7.1)
Fatigue	22	(2.6)	37	(4.4)
Nervous system disorders	36	(4.2)	47	(5.5)
Headache	25	(2.9)	25	(3.0)
Dizziness	7	(0.8)	12	(1.4)
Skin and subcutaneous tissue disorders	19	(2.2)	28	(3.3)
Rash	6	(0.7)	10	(1.2)
Infections and infestations	24	(2.8)	27	(3.2)
Hepatitis B	15	(1.8)	9	(1.1)
Musculoskeletal and connective tissue disorders	18	(2.1)	18	(2.1)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.3.2.1]

Medical Officer Comments: *As noted previously, the assessment of relationship of an adverse event by the investigator to study medication is subjective, and this analysis will be considered only in context of all the other safety data for telbivudine.*

7.4.2 Laboratory Findings

New-onset, Grade 3 or 4 laboratory abnormalities in the pooled major safety population showed a similar pattern to that reported in the individual studies. As shown in the following table, a higher proportion of telbivudine- than lamivudine-treated patients had Grade 3 or 4 CK elevations; while Grade 3 or 4 AST and ALT elevations were reported in a higher proportion of lamivudine than telbivudine-treated patients. There also were numerically more patients in the lamivudine group with Grade 3 or 4 lipase elevations, decreased hemoglobin, decreased platelet count and increased total bilirubin.

Table 129. New-Onset Grade 3/4 Laboratory Abnormalities in Major Safety Population

Table 5-3 On-treatment, new-onset Grade 3/4 hematologic and chemistry abnormalities – Pooled NV-02B-007/NV-02B-015

Laboratory Test	Lamivudine (N=852) n (%)	Telbivudine (N=847) n (%)
Absolute neutrophils	15 (1.8)	14 (1.7)
ALT (SGPT)	112 (13.1)	57 (6.7)
Amylase	3 (0.4)	2 (0.2)
AST (SGOT)	85 (10.0)	53 (6.3)
Creatine kinase (CK)	34 (4.0)	107 (12.6)
Hemoglobin	2 (0.2)	0
Lipase	35 (4.1)	20 (2.4)
Platelet count	8 (0.9)	5 (0.6)
PT	3 (0.4)	4 (0.5)
Total bilirubin	6 (0.7)	1 (0.1)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.4.1.2]

7.4.3 Vital Signs

See Section 5.3 Individual Studies.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not routinely performed in studies 007 or 015.

7.4.5 Special Safety Studies

Special Safety Studies were not performed.

7.4.6 Immunogenicity

As reviewed for the original NDA 22-011, there was no evidence for immunogenicity of telbivudine which is a small molecule which is not expected to be immunogenic. No additional information regarding immunogenicity was provided with this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose-ranging studies were submitted with NDA 22-011 S-001 or NDA 22-154. As reviewed for the original NDA 22-011, both exposure- and dose-based approached indicated a near maximal virologic response with telbivudine doses in the range of 400-800 mg/day.

7.5.2 Time Dependency for Adverse Events

Adverse Events by Duration of Therapy
For analysis of adverse events by treatment duration (52 or 104 weeks) in the phase 3 studies, see Section 5.3 Individual Studies.

Additionally, the applicant included an analysis of adverse events in patients who received more than 104 weeks of telbivudine treatment for the pooled major safety population. This analysis was performed by evaluating the subset of patients who received telbivudine in studies 007 and 015, subsequently enrolled in study 022, and completed the 022 study or discontinued prematurely by the data cutoff date of December 31, 2006. The applicant's analysis of adverse events (by SOC) and by treatment year are shown in the following table. Year 1 and 2 refer to the time periods when patients were enrolled in studies 007 or 015, and Year 3 and 4 refer to the time periods when patients were enrolled in study 022. In this analysis, the proportion of telbivudine patients who experienced any adverse event decreased from year 1 to year 4. The most common SOC in which adverse events were reported was Infections and Infestations, Gastrointestinal disorders, Nervous system disorders, General and site administration disorders, Investigations and Musculoskeletal and Connective tissue disorders. The incidence of adverse events in these SOCs decreased from Year 1 to Year 3 on telbivudine with the exception of Nervous system disorders which increased from Year 2 (8%) to Year 3 (12%).

Table 130. Adverse Events by Year in Patients from Studies 007 and 015 who subsequently enrolled in Study 022

Table 4-12 Summary of on-treatment adverse events by system organ class, cumulative (>2%) and by year – NV-02B-007 and NV-02B-015 patients on telbivudine who entered NV-02B-022

System Organ Class	Year 1[1] N=75 n (%)	Year 2[1] N=75 n (%)	Year 3 N=74 n (%)	Year 4 N=9 n (%)	Total N=75 n (%)
Patients reporting an adverse event	55 (73.3)	45 (60.0)	37 (50.0)	3 (33.3)	63 (84.0)
Infections and infestations	20 (26.7)	20 (26.7)	10 (13.5)	0	31 (41.3)
Gastrointestinal disorders	21 (28.0)	14 (18.7)	12 (16.2)	0	30 (40.0)
Nervous system disorders	12 (16.0)	6 (8.0)	9 (12.2)	0	23 (30.7)
General disorders and administration site conditions	11 (14.7)	11 (14.7)	9 (12.2)	1 (11.1)	22 (29.3)
Investigations	10 (13.3)	10 (13.3)	7 (9.5)	1 (11.1)	19 (25.3)
Musculoskeletal and connective tissue disorders	10 (13.3)	6 (8.0)	5 (6.8)	0	17 (22.7)
Skin and subcutaneous tissue disorders	10 (13.3)	4 (5.3)	1 (1.4)	1 (11.1)	15 (20.0)
Injury, poisoning and procedural complications	6 (8.0)	6 (8.0)	4 (5.4)	0	12 (16.0)
Respiratory, thoracic and mediastinal disorders	5 (6.7)	3 (4.0)	3 (4.1)	0	10 (13.3)
Metabolism and nutrition disorders	5 (6.7)	3 (4.0)	0	0	6 (8.0)
Psychiatric disorders	3 (4.0)	3 (4.0)	1 (1.4)	0	6 (8.0)
Eye disorders	2 (2.7)	3 (4.0)	1 (1.4)	0	5 (6.7)
Vascular disorders	3 (4.0)	1 (1.3)	1 (1.4)	0	5 (6.7)
Reproductive system and breast disorders	1 (1.3)	1 (1.3)	2 (2.7)	0	4 (5.3)
Cardiac disorders	2 (2.7)	0	1 (1.4)	0	3 (4.0)
Ear and labyrinth disorders	1 (1.3)	2 (2.7)	1 (1.4)	0	3 (4.0)
Hepatobiliary disorders	2 (2.7)	2 (2.7)	0	0	3 (4.0)
Renal and urinary disorders	2 (2.7)	1 (1.3)	1 (1.4)	0	3 (4.0)
Blood and lymphatic system disorders	2 (2.7)	0	0	0	2 (2.7)

[1] Data for Years 1 and 2 are from the previous study.

Source: Table 4-12 Summary of Clinical Safety

Medical Officer Comments: *Datasets for the ongoing study 022 were not available for review to confirm these findings. Additionally, the number of patients who completed or discontinued study 022 in Year 4 was too small for any meaningful analysis.*

Musculoskeletal adverse events were summarized by duration of telbivudine treatment as follows:

Table 131. Selected Adverse Events by Treatment Year in Telbivudine-treated Patients initially enrolled in studies 007 and 015 (Years 1 and 2) and subsequently enrolled in Study 022 (Years 3 and 4)

Adverse Event (Preferred Term)	Year 1 N=75	Year 2 N=75	Year 3 N=74
Myalgia	2 (2.7)	3 (4.0)	0
Pain in extremity	3 (4.0)	1 (1.4)	0
Myopathy	0	0	0
Myositis	0	0	0
Peripheral neuropathy	0	0	0
Elevated CK	7 (9.3)	3 (4.0)	1 (1.4)

Medical Officer Comments: *The number of patients in this subset is small, and no conclusions can be drawn regarding emergence of adverse events over time in this analysis, although there was no increase in the proportion of patients who experienced these events from Year 1 or 2 to Year 3. No adverse events in this category were reported in Year 4 among 9 patients.*

The applicant also evaluated adverse events leading to telbivudine discontinuation over the 4 year time period. In this analysis, for Years 1 and 2, discontinuations due to adverse events are reported for all telbivudine-treated patients in studies 007 and 015; while numbers for Years 3 and 4 represent the subset of patients who received telbivudine in studies 007 or 015 and subsequently enrolled in study 022, and completed that study, or discontinued that study prematurely. As shown in the following table, the proportion of patients who discontinued telbivudine due to adverse events increased from study Year 1 to Year 3 (0.7% to 10.8%).

Table 132. Adverse Events resulting in Treatment Discontinuation by Year

Table 4-13 Summary of on-treatment adverse events causing drug discontinuation by year – NV-02B-007 and NV-02B-015 patients on telbivudine who entered NV-02B-022

Preferred Term	Year 1[1] N=847 n (%)	Year 2[1] N=827 n (%)	Year 3 N=74 n (%)	Year 4 N=9 n (%)	Total N=847 n (%)
Patients reporting an adverse event	6 (0.7)	4 (0.5)	8 (10.8)	1 (11.1)	19 (2.2)
Hepatitis B	0	2 (0.2)	1 (1.4)	0	3 (0.4)
Nausea	2 (0.2)	0	1 (1.4)	0	3 (0.4)
Fatigue	1 (0.1)	0	1 (1.4)	0	2 (0.2)
Alanine aminotransferase increased	0	0	1 (1.4)	1 (11.1)	2 (0.2)
HBV DNA increased	0	0	2 (2.7)	0	2 (0.2)
Uncoded[2]	0	0	2 (2.7)	0	2 (0.2)
Abdominal distension	1 (0.1)	0	0	0	1 (0.1)
Abdominal pain upper	0	0	1 (1.4)	0	1 (0.1)
Cardiac failure congestive	0	1 (0.1)	0	0	1 (0.1)
Loose stools	1 (0.1)	0	0	0	1 (0.1)
Vomiting	0	0	1 (1.4)	0	1 (0.1)
Hepatic failure	0	1 (0.1)	0	0	1 (0.1)
Aspartate aminotransferase increased	0	0	0	1 (11.1)	1 (0.1)
Blood creatine phosphokinase increased	1 (0.1)	0	0	0	1 (0.1)
Myopathy	1 (0.1)	0	0	0	1 (0.1)
Pain in extremity	1 (0.1)	0	0	0	1 (0.1)
Sjogren's syndrome	0	0	1 (1.4)	0	1 (0.1)
Spinal muscular atrophy	0	0	1 (1.4)	0	1 (0.1)
Murder	1 (0.1)	0	0	0	1 (0.1)

[1] Data for Years 1 and 2 are from the previous study.
[2] 2 patients with uncoded AEs as data is preliminary.

Medical Officer Comments: *The numbers of patients who rolled over into study 022 and then completed or prematurely discontinued that study are small (75 patients for year 3; 9 patients in Year 4). There does not appear to be any trend of increased frequency for specific adverse events leading to discontinuation of treatment by Year 3, except possibly for the 2 patients who discontinued due to increased HBV DNA in year 3 compared to no discontinuation for that event in Years 1 and 2.*

7.5 3 Drug-Demographic Interactions

Adverse Events by Age

The applicant performed subgroup analysis of adverse events by age, gender, and race using the pooled major safety population (Studies 007 and 015). In the applicant's analysis, the incidence adverse events occurring up to 30 days after treatment discontinuation was proportionately higher with increasing age. From the applicant's summary tables, adverse events (common or significant adverse events) were examined for effect of age as shown in the following table. The proportion of patients with increased ALT decreased with age in the telbivudine group, and increased with age in the lamivudine group, and the converse was noted for CK elevation. The incidence of arthralgia increased with age; whereas the incidence of myalgia increased only

slightly with age in both treatment groups. There were too few events of myopathy, myositis, or polyneuropathy to analyze by age; and hypoaesthesia increased only slightly with age in the telbivudine group. Headache increased with age in both treatment groups, as did dizziness, the latter, more so in the lamivudine group. The incidence of cough also increased slightly with age in both groups, but to a greater extent in the telbivudine group. The following is not an exhaustive review of all adverse events by age.

Table 133. Selected Adverse Events by Patient Age in Pooled Major Safety Population (Studies 007 and 015)

Adverse Event (Preferred Term)	Lamivudine Age < 30 N=329	Lamivudine Age 30-50 N=415	Lamivudine Age > 50 N=108	Telbivudine Age < 30 N=352	Telbivudine Age 30-50 N= 404	Telbivudine Age > 50 N=91
Patients reporting an AE	226 (68.7)	316 (76.1)	252 (81.5)	252 (71.6)	329 (81.4)	78 (85.7)
ALT increased	8 (2.4)	17 (4.1)	6 (5.6)	18 (5.1)	7 (1.7)	2 (2.2)
CK increased	27 (8.2)	20 (4.8)	5 (4.6)	38 (10.8)	36 (8.9)	16 (17.6)
Arthralgia	6 (1.8)	19 (4.6)	13 (12.0)	5 (1.4)	21 (5.2)	11 (12.1)
Myalgia	3 (0.9)	11 (2.7)	3 (2.8)	9 (2.6)	14 (3.5)	4 (4.4)
Myopathy	0	0	0	0	1 (0.2)	1 (1.1)
Myositis	0	1 (0.2)	0	0	1	1
Dizziness	6 (1.8)	24 (5.8)	13 (12.0)	9 (2.6)	18 (4.5)	5 (5.5)
Headache	26 (7.9)	55 (13.3)	14 (13.0)	15 (4.3)	52 (12.9)	16 (17.6)
Hypoaesthesia	2 (0.6)	6 (1.4)	1 (0.9)	0	6 (1.5)	3 (3.3)
Paraesthesia	0	5 (1.2)	1 (0.9)	1 (0.3)	1 (0.2)	0
Polyneuropathy	0	0	0	0	1 (0.2)	1 (1.1)
Cough	12 (3.6)	26 (6.3)	7 (6.5)	12 (3.4)	32 (7.9)	8 (8.8)
Nausea	10 (3.0)	3 (0.7)	1 (0.9)	0	5 (1.2)	0
Vomiting	4 (1.2)	12 (2.9)	2 (1.9)	8 (2.3)	7. (1.7)	1 (1.1)

Source: Table 14.3.1.3.5.1 Clinical Summary of Safety

Medical Officer Comments: *Because this was a sub-group analysis and the numbers of patients > 50 years old was small in these studies, any conclusions regarding the association of specific adverse events with age can only be considered preliminary.*

Adverse Events by Gender

The applicant also analyzed adverse events in the pooled major safety population (Studies 007 and 015) by gender. Overall, the proportion of patients with any adverse event was similar for males and females within treatment groups. From the applicant's summary tables, selected adverse events (some common or significant adverse events) were examined for gender effect as shown in the following table. The proportion of patients with CK elevations was higher among males than females in both treatment groups; while the proportion of ALT elevations was similar for males and females. Proportionately more females than males experienced dizziness, headache, cough in both treatment groups; while a higher proportion of females experienced

arthralgias and vomiting in the lamivudine groups, and vice versa for the telbivudine group. The following is not an exhaustive review of all adverse events by gender.

Table 134. Adverse Events by Gender in the Pooled Major Safety Population

Adverse Event (Preferred Term)	Lamivudine Male N=654	Lamivudine Female N=198	Telbivudine Male N=642	Telbivudine Female N=205
Patients reporting an AE	480 (73.4)	150 (75.8)	498 (77.6)	161 (78.5)
ALT increased	24 (3.7)	7 (3.5)	21 (3.3)	6 (2.9)
CK increased	45 (6.9)	7 (3.5)	76 (11.8)	14 (6.8)
Arthralgia	24 (3.7)	14 (7.1)	31 (4.8)	6 (2.9)
Myalgia	10 (1.5)	7 (3.5)	21 (3.3)	6 (2.9)
Myopathy	0	0	2 (0.3)	0
Myositis	1 (0.2)	0	2 (0.3)	0
Dizziness	23 (3.5)	20 (10.1)	21 (3.3)	11 (5.4)
Headache	66 (10.1)	20 (14.6)	56 (8.7)	27 (13.2)
Hypoaesthesia	6 (0.9)	3 (1.5)	6 (0.9)	3 (1.5)
Paraesthesia	4 (0.6)	2 (1.0)	2 (0.3)	2 (1.0)
Polyneuropathy	0	0	1 (0.2)	1 (0.5)
Cough	30 (4.6)	15 (7.6)	37 (5.8)	15 (7.3)
Nausea	20 (3.1)	20 (10.1)	32 (5.0)	13 (6.3)
Vomiting	10 (1.5)	8 (4.0)	9 (1.4)	7 (3.4)

Source: Table 14.3.1.3.5.2 Summary of Clinical Safety

Adverse Events by Race

In the applicant's analysis of adverse events by race in the pooled major safety population (Studies 007 and 015), the overall proportion of patients with any adverse event was similar among Caucasians, Asians, and "other" races in lamivudine-treated patients, but was somewhat higher in "other" races than in Caucasians or Asians among telbivudine-treated patients. From the applicant's summary tables, selected adverse events (some common or significant adverse events) were examined for differences by race as shown in the following table.

Table 135. Adverse Events by Race in the Pooled Major Safety Population

Adverse Event (Preferred Term)	Lamivudine Caucasian N=111	Lamivudine Asian N=680	Lamivudine "Other" N=61	Telbivudine Caucasian N=98	Telbivudine Asian N=692	Telbivudine "Other" N=57
Patients reporting an AE	82 (73.9)	500 (73.5)	48 (78.7)	72 (73.5)	535 (77.3)	52 (91.2)
ALT increased	24 (21.6)	69 (10.1)	17 (27.9)	29 (29.6)	93 (13.4)	19 (33.3)
CK increased	13 (11.7)	30 (4.4)	9 (14.8)	22 (22.4)	53 (7.7)	15 (26.3)
Arthralgia	10 (21.6)	85 (12.5)	14 (23.0)	21 (21.4)	97 (14.0)	14 (24.6)
Myalgia	1 (0.9)	14 (2.1)	2 (3.3)	3 (3.1)	21 (3.0)	3 (5.3)
Myopathy	0	0	0	0	2 (0.3)	0
Myositis	0	1 (0.1)	0	0	1 (0.1)	1 (1.8)
Dizziness	3 (2.7)	36 (5.3)	4 (6.6)	1 (1.0)	3 (0.4)	2 (3.5)
Headache	22 (19.8)	63 (9.3)	10 (16.4)	22 (22.4)	53 (7.7)	8 (14.0)
Hypoaesthesia	0	7 (1.0)	2 (3.3)	2 (3.0)	5 (0.7)	2 (3.5)
Paraesthesia	1 (0.9)	4 (0.6)	1 (1.6)	1 (1.0)	2 (0.3)	1 (1.8)
Polyneuropathy	0	0	0	1 (1.0)	1 (0.1)	0
Cough	2 (1.8)	39 (5.7)	4 (6.6)	4 (4.1)	45 (6.5)	3 (5.3)
Nausea	6 (5.4)	29 (4.3)	5 (8.2)	6 (6.1)	32 (4.6)	7 (12.3)
Vomiting	1 (0.9)	16 (2.4)	1 (1.6)	3 (3.1)	11 (1.6)	2 (3.5)

Source: Table 14.3.1.3.5.2 Summary of Clinical Safety

Medical Officer Comments: *Note that the term, "other" races is not defined in the submission with regard to the major safety population, and thus it is not clear whether this includes patients of African American, Hispanic or other descent. It was noted previously that the proportion of patients with any adverse event was lower in the 015 study, which included only Chinese patients, than in the 007 study, for reasons unknown. In this analysis of adverse events by race, overall adverse events and many of the selected events were less common in patients of Asian descent in both treatment groups (e.g. ALT and CK increase, arthralgia, headache, and nausea). Whether this is due to differences in reporting by the investigator, by differences in patient reporting adverse events, or due to racial differences, is not clear.*

7.5 4 Drug-Disease Interactions

In the pivotal study (007) and supportive study (015) all patients had chronic hepatitis B, and compensated liver disease. HIV- or HCV-co-infected patients were not included in these studies. Thus, safety of telbivudine in patients co-infected with HIV, HCV, or HDV has not been evaluated. Additionally, only preliminary blinded safety data is available from Study NV-02B-011, evaluating telbivudine in patients with chronic hepatitis B and decompensated liver disease. In Study 007, the proportion of patients who experienced at least one adverse event was slightly higher in the HBeAg-negative subpopulation (197/235, 83.8%), than in the HBeAg-positive subpopulation (354/445, 79.6%).

7.5.5 Drug-Drug Interactions

In study NV-02B-028 which evaluated potential pharmacokinetic interactions between telbivudine and tenofovir in healthy subjects, no significant pharmacokinetic interaction was demonstrated. Safety data from this study was reviewed in section 5.3 Individual Studies. No new safety issues were identified in this study.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted. Telbivudine's preclinical profile indicates that this drug does not pose a risk of carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancies in Clinical Trials
The applicant summarized pregnancies and outcomes reported through August 31, 2007 for patients exposed to telbivudine in a clinical trial, a total of 64 patients, 35 of whom were exposed to telbivudine directly, and 29 exposed indirectly via a male partner who received telbivudine were identified. Of the 35 "in utero" exposures, outcome was unknown at the time of submission in 20; and of the 29 indirect exposures, outcome was unknown in 6. The following table summarizes the outcomes of these pregnancies.

Table 136. Pregnancies reported in Telbivudine Clinical Trials

Table 9-1 Reports of pregnancies in patients exposed to telbivudine in a clinical trial

Pregnancy Outcome	Exposure *in utero*	Exposure via father
Spontaneous abortion	3	2
Elective termination (fetal defects)	1	0
Elective termination (no fetal defects or unknown)	12	6
Live birth with congenital anomaly	0	1
Live birth without congenital anomaly	5	14
Outcome unknown	14	6
Total	35	29

Source: Table 9-1 Summary of Clinical Safety

One elective termination with fetal defects and one live birth with a congenital abnormality was reported. Brief summaries of these cases were provided and are reviewed below:

Patient 005-061 (Study NV-02B-022): This was a 28 year-old female, gravida 2, para 1 who sought medical consultation at 16 weeks of pregnancy. She had been treated with telbivudine for 4 months in study 022, although it is not clear which study medication she received before roll-over into 022. At 16 weeks, an ultrasound suggested a molar pregnancy, and an HCG level was 225,000 mIU/mL. The patient underwent suction evacuation of the pregnancy the same day. Histopathological results were not available.

Patient 051-009 (NV-02B-022): This pregnancy was reported in a female partner of a male patient. Delivery was uncomplicated at 41 weeks, and the infant was born with a congenital hip dislocation. No further details were available.

Postmarketing Reports of Pregnancies
In the Periodic Safety Update (PSUR)-2, for the reporting period (March 1, 2007 to August 31, 2007), 13 prospective cases of telbivudine exposures during pregnancy were reported. The outcomes on 12 of these cases was unknown at the time of the report, and in 1 case, the newborn was normal. Additionally, two retrospective cases were reported. The first was that of a 30-year old female with chronic hepatitis B who took telbivudine for approximately one month in the third trimester of pregnancy to prevent HBV transmission to the infant. The delivery was uncomplicated, and the patient continued telbivudine while breastfeeding the newborn. The neonate received anti-hepatitis B immunoglobulin and hepatitis B vaccines within two hours of birth. The newborn experienced a single episode of apnea approximately 36 hours after birth. The patient (mother) stopped the telbivudine and breast feeding after this event, and no further episodes of apnea were reported. According to the patient's report, an MRI of the infant's brain showed "brain damage" per the consumer report. This case was also summarized as a serious report in Postmarketing Adverse Events.

Medical Officer Comments: *In this latter case, any potential contribution of telbivudine to the episode of apnea is difficult to assess because post-delivery the newborn had also received hepatitis B vaccine and anti-hepatitis B immunoglobulin. Additionally, the Apgar score at birth was not provided.*

The second case was that of a female patient enrolled in an Idenix-sponsored study of telbivudine for treatment of chronic hepatitis B. The patient withdrew from the study after one year because pregnancy was confirmed. At approximately 6 weeks, the patient experienced vaginal "spotting" and the pregnancy was terminated due to "threatened abortion". The applicant also reported a case of an elective termination with an abnormality (a benign hydatidiform mole) in a fetus exposed to telbivudine in the first trimester of pregnancy.

Medical Officer Comments: *It is not clear whether this latter report of the benign hydatidiform mole is the same as that described above in a patient from study 022.*

Antiretroviral Pregnancy Registry (APR)
APR is an ongoing, international registry intended to provide an early signal of any major teratogenic effect associated with prenatal exposure to the monitored antiretroviral drugs when administered to pregnant women. The registry started systematically collecting data on hepatitis B since January 2003. Sebivo/Tyzeka has been included in the registry, and there were no reports of women exposed since it's inclusion in the registry as of the cut-off date (August 31, 2007) for PSUR-3.

Medical Officer Comments: *Telbivudine was not found to teratogenic in preclinical studies. Currently telbivudine is listed as a pregnancy category B drug, and at this time, none of the evidence provided from telbivudine exposures in pregnancy suggests that telbivudine causes a specific fetal defect or congenital abnormality. No change in the pregnancy labeling category is recommended at this time.*

7.6.3 Pediatrics and Effect on Growth
Not applicable. Studies in pediatric patients have not been performed to date.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information on overdose, abuse potential withdrawal or rebound was submitted with NDA 22-011 S-001 or NDA 22-154.

7.7 Additional Submissions

The 120- Safety Update to this supplemental NDA was submitted on May 30, 2008, and is reviewed in this section. However, safety information regarding deaths, and serious or significant adverse events from recently completed or ongoing clinical studies was reviewed in Section 7 above.

Preclinical Observations
No new preclinical information was submitted with the supplemental NDA. Since that time, in response to a postmarketing study commitment, on March 28, 2008, the applicant submitted two preclinical study reports which evaluated the potential for mitochondrial toxicity of telbivudine.

In IDIX-07-116A, "In vitro assessment of mitochondrial toxicity in normal primary human skeletal muscle cells following telbivudine exposure", mitochondrial toxicity was not observed. However, in this study, lactic acid concentrations were not elevated in one positive control, zidovudine, and the applicant believes that the assay conditions may not have been optimized to detect subtle effects, and that the potential for mitochondrial toxicity with telbivudine cannot be excluded based on this study. The applicant plans to perform further studies in human skeletal muscles cells and other in vitro systems.

The second study, IDIX-07-116B, "In vitro assessment of mitochondrial toxicity in primary human hepatocytes following telbivudine exposure", mitochondrial toxicity was not demonstrated with telbivudine or with the positive controls. The applicant concluded that

cultured human hepatocytes may not be a suitable model for assessment of mitochondrial toxicity.

Medical Officer Comments: *Because the mechanism of muscle and nerve injury resulting in myopathy and/or peripheral neuropathy has not been elucidated, additional in vitro studies in this regard will be encouraged.*

Safety Information from Clinical Studies

The 120-day safety update includes safety information from the following studies which were recently completed:

Table 137. Key Clinical Studies with Safety Data in 120-Day Safety Update

Table 1-1 Summary of studies providing key safety data in the 120-day safety update

Study No.	Study objective, population	Enrolled/ planned patients	Safety population	Planned treatment duration	Telbivudine dosage	Type of comparator	Cut-off date
NV-02B-019	Assess antiviral efficacy of switching lamivudine-treated patients to telbivudine or continuing lamivudine patients. Population: adults with CHB	248	246	52 weeks	600 mg daily	Lamivudine (100 mg)	Completed

Study No.	Study objective, population	Enrolled/ planned patients	Safety population	Planned treatment duration	Telbivudine dosage	Type of comparator	Cut-off date
NV-02C-004	To compare the antiviral efficacy of the combination of telbivudine + valtorcitabine to telbivudine monotherapy Population: adults with CHB	134/130	132	52 weeks	600 mg daily	Telbivudine (600 mg) + valtorcitabine (750 mg)	completed

NV is Idenix-assigned. CLDT600A is Novartis-assigned study number

Source: 120-Day safety Update

Brief Summary of Recently Completed Studies

NV-02B-019: This study was recently completed, randomized trial in 248 patients with chronic hepatitis B who were previously treated with lamivudine for 3-12 months and were then assigned to switch to telbivudine or continue lamivudine for 1 year. The median patient age was 35 years old, 76% patients were male, and the majority (61%) of patients were of Asian descent. A total of 246 patients were enrolled in the study, and overall 94% patients completed the study. The median telbivudine exposure was 364 days, with 88% patients receiving > 360 days telbivudine.

NV-02C-004: This is a recently completed, randomized, blinded trial of telbivudine vs. telbivudine plus valtorcitabine (LdC) in HBeAg-positive patients with chronic hepatitis B for 1 year. A total of 132 patients were enrolled. Median patient age in this study was 30 years old, 70% of patients overall were males; and 92% were of Asian descent. Median telbivudine exposure in this study was 52 weeks. Approximately 95% patients overall completed the study.

Safety information from ongoing clinical studies was also submitted with the 120- Day Safety Update. These studies are listed in the following table. Note that Study CLDT600A2406 was recently stopped due to the occurrence of peripheral neuropathy in a substantial proportion of patients in the telbivudine plus pegylated interferon combination arm. Study NV-02B-011 in patients with decompensated liver disease is ongoing, and safety data from that study remain blinded to treatment arm. Study NV-02B-022, which is the follow-on open-label, long-term safety study of telbivudine for treatment of chronic hepatitis B in patients previously enrolled in other Novartis or Idenix-sponsored telbivudine studies, remains ongoing.

Table 138. Other Clinical Studies with Safety Data in 120-Day Safety Update

Table 1-2 Summary of other clinical studies in 120-day safety update

Study No.	Study objective, population	Enrolled/ Planned patients	Safety population	Planned treatment duration	Telbivudine dosage	Type of comparator	Cut-off date
NV-02B-011/ CLDT600A 2301[1] (double-blind)	To compare antiviral efficacy, safety, and tolerability of telbivudine to lamivudine Population: adults with decompensated CHB	240	232	104 weeks	600 mg	lamivudine	Dec-31-2007
CLDT600A 2406	Comparing the safety and efficacy of combination telbivudine+ Pegasys® with Pegasys® monotherapy and telbivudine monotherapy Population: adults with HBeAg positive CHB	159/300	152	104 weeks	600 mg	Pegasys® 180ug	Feb-29-2008
NV-02B-022/ CLDT600A 2303[1]	An Open Label Trial of Telbivudine (LdT) in Adults with CHB Previously Treated in Idenix-Sponsored Telbivudine Studies	2100	667*	104 weeks	600 mg	none	Dec-31-2007

[1] NV is Idenix-assigned study number, CLDT600A is Novartis-assigned study number
* patients enrolled in NV-02B-007 and NV-02B-015 who rolled into NV-02B-022/ CLDT600A2303

Brief Summary of Ongoing Studies

CLDT600A2406: This is an open-label, controlled 2-year study designed to evaluate efficacy and safety of telbivudine monotherapy vs. telbivudine plus pegylated interferon-alfa-2a vs. pegylated interferon-alfa-2a alone in adult patients with HBeAg-positive chronic hepatitis B. The Data Safety Monitoring Board (DSMB) met in December, 2007 after initial review of peripheral neuropathy events; and upon receipt of additional cases of peripheral neuropathy in the combination arm, the DSMB and applicant decided to stop enrollment and discontinue the combination arm due to an unanticipated increased risk of peripheral neuropathy in that treatment group. Since the study could no longer meet its primary objectives, all patients were discontinued on May 15, 2008. In the 120-Day safety report, the data was presented as blinded to treatment arm.

In study CLDT600A2406, 159 patients were enrolled. The median patient age was 34 years old, 68% patients were male; 53% were Asian, 38% Caucasian, 5% Black, 4% Pacific Islander, and 1% other racial/ethnic designation. At the time of the cut-off date for this study, February 29, 2008, 28% patients had discontinued the study. Discontinuations due to adverse events were reported in 45/159 (28%). Discontinuations due to sponsor withdrawal of patients in telbivudine/pegylated interferon-alfa-2a arm occurred in 28/159 (18%), due to unsatisfactory therapeutic effect in 3/159 (2%), due to withdrawal of consent in 1 subject, and due to protocol deviation in 1 subject and missing data for 2 subjects.

NV-02B-011/CLDT600A2303: This study is an ongoing open-label study evaluating long-term safety of telbivudine in patients rolled over from other Novartis and Idenix phase III studies. A total of 232 patients were enrolled up to the cut-off date of February 29, 2008. The median patient age was 52 years old; the majority of patients were males (73%), and of Asian descent (65%). Median telbivudine exposure was 84 weeks in this study. To the cut-off date, 33% patients had completed the study, 27% were continuing, and 40% had discontinued the study. The most common reasons for study discontinuation was death, reported in 27/232 (11.6%), virologic breakthrough in 24/232 (10%), request of patient, investigator or sponsor in 12/232 (5%), adverse events in 8/232 (3%), and treatment failure in 8 (3%).

Medical Officer Comments: *Note that in this study, 34 patient deaths were reported, but death was reported as the reason for discontinuation in 27.*

An overall summary of safety data for telbivudine from the recently completed and ongoing studies is summarized in the following table.

Table 139. Summary of Safety Information from Recently Completed and Ongoing Studies

Parameter	Study NV-02B-019	Study NV-02B-004	Study CLDT600A2406*	Study NV-02B-011/CLDT600A2301	Study NV-02B-022/CLDT600A2303
Population	CHB	HBeAg+ CHB	HBeAg+ CHB	Decompensated CHB	CHB-rollover open-label LdT study
Comparator(s)	lamivudine	LdT + LdC	LdT + Pegasys; Pegasys alone	lamivudine	none
N	246 122-LdT 124- Lam	132 64-LdT 68-LdT+LdC	159 overall enrolled pop.	232 overall	>1800
Patient Deaths	1-Lam	0	0	34 (14%) overall	Not reported
Patients with SAEs	5-LdT 8-Lam	3-LdT 4-LdT+LdC	Not reported	108 (46.6%) overall	Not reported
Discontinuations due to AE	1-LdT 1-Lam	0-LdT 1-LdT + LdC	10 (6.3%) due to AEs 28 (17.6%) administrative	8 (3.4%) due to AE 27 (11.6%) due to death	Not reported
Peripheral Neuropathy	0	3-LdT 0- LdT + LdC	1-LdT monotherapy 7-combination	6- blinded	3-LdT
ALT flares (ALT > 2x baseline and > 10 x ULN)	3-LdT 4-Lam	Not analyzed	8-(blinded)	1- (blinded)	23-LdT
Musculoskeletal AEs	19-LdT 12-Lam	5-LdT 10-LdT +LdC	Not reported	88 (blinded)	Not reported
CK elevation (as AE)	0	0	Not reported	7 (blinded)	Not reported

Other safety findings		Combination arm: mild to mod decreased Hob in first 4 weeks; 2 discontinuations due to anemia		93 (40.1%) patients discontinued study; 27 (11.6%) discontinued due to death	

*Combination arm stopped January 8, 2008 due to increased risk of peripheral neuropathy in the combination arm. Study stopped May 15, 2008 because study objectives could not be met.
LdT= telbivudine
CHB= chronic hepatitis B

Deaths

No deaths were reported in Studies 004 or CLDT600A2406. Deaths reported in the other studies are summarized below from the narratives provided in the Safety Update.

Study NV-02B-019

One death was reported in this study. The patient was a 44 year old Tongan male with a history of ischemic heart disease. Study drug (lamivudine) was initiated March 31, 2005, and date of discontinuation was unknown. The patient was last seen at his week 40 study visit (January 12, 2006), and he was reportedly doing well and had a good response to treatment. The study coordinator was informed of his death on March 13, 2006. According to the patient's medical provider, the patient had died unexpectedly on [redacted], reportedly collapsing and dying during training for a triathlon. An autopsy was not performed. The suspected cause of death (per the investigator) was cardiac arrest; or less likely a pulmonary embolus following an airplane flight. b(6)

Medical Officer Comments: *This patient reportedly had a history of ischemic heart disease, although no details were provided. Any relationship to study medication (lamivudine) seems unlikely in this case.*

Study NV-02B-011/CLDT600A2301

The applicant provided information regarding the deaths that occurred in this study in patients with decompensated liver disease, as shown in the following table. However, the study is ongoing, and the data remain blinded to treatment group.

Table 140. Deaths in Study 011

Table 3-17 Listing of all deaths in NV-02B-011/ CLDT600A2301 (cut off date 29 Feb 2008) (safety population)*

Center/patient	Study day of last dose	Date of death	Study day of death	Prinicipal cause (preferred term)
13/007	351	[redacted]	351	Hepatic neoplasm malignant
18/007	125		125	Hepatic cirrhosis
18/012	718		720	Neoplasm benign
18/014	539		564	Necrotizing fasciitis
18/029	265		296	Hepatitis B
20/002	92		296	Hepatic failure
24/009	146		162	Sepsis
24/011	273		276	Septic shock
25/001	481		482	Pneumonia aspiration
29/006	86		86	Septic shock
29/007	9		13	Peritonitis bacterial
29/015	242	[redacted]	243	Septic shock

b(6)

b(6)

b(6)

Center/patient	Study day of last dose	Date of death	Study day of death	Principal cause (preferred term)
33/007	344	[redacted]	450	Hepatic neoplasm malignant
34/006	834		470	Gastrointestinal hemorrhage, Jaundice, and Pallor
4/006	418		419	Cerebral hemorrhage
41/007	86		87	Hepatic encephalopathy
56/002	451		462	Hepatic failure, Ascites, and Hernia
65/010	845		847	Septic shock
66/002	466		466	Hepatorenal syndrome
71/001	717		717	Pneumonia, Hepatic Coma, and Ascites
71/008	586		586	Esophageal varices hemorrhage
76/001	62		62	Hepatic cirrhosis
80/004	54		57	Sepsis
84/015	430		432	Sepsis
85/017	105		106	Esophageal varices hemorrhage
86/014	62		64	Enteritis
86/015	179		183	Depressed level consciousness
86/017	210		229	Hepatic encephalopathy
87/009	282		282	Sepsis
87/018	193		194	Gastrointestinal hemorrhage
87/029	496		500	Death
89/017	9		10	Hepatorenal syndrome
89/024	35	[redacted]	43	Hemorrhage
91/004	545	[redacted]	551	Hepatorenal syndrome

b(6)

* In 34 patients death was reported an AE, however for 27 patients death was reported as the reason for discontinuation (Table 2-10)

note: database cleaning is ongoing

Source: NV-02B-011/ CLDT600A2301 Listing 3-2

Medical Officer Comments: *As the applicant has noted, the increased incidence of deaths in this study is not unexpected in this population with decompensated liver disease. The Medical Officer agrees that none of the causes of death listed above would be unexpected in this population, as patients with decompensated liver disease are at high risk for hepatic failure, serious infections, gastrointestinal bleeding, encephalopathy or coma, and hepatorenal syndrome. However, before drawing any conclusions, we will await the receipt of the unblended data from this study.*

Non-fatal Serious Adverse Events
Study NV-02C-004

Similar proportions of patients had a serious adverse event in this study. As shown in the following the pattern of serious adverse events differed with telbivudine alone vs. telbivudine plus valtorcitabine.

Table 141. Non-Fatal Serious Adverse Events in Study 004

Table 3-8 Summary of Serious Adverse Events other than Death in NV-02C-004 (safety population)

Event	LDT N=64 n (%)	LDT+LDC N= 68 n (%)
Number pts reporting an AE	3 (4.7)	4 (5.9)
Abdominal pain	0	2 (2.9)
Pancreatitis	0	1 (1.5)
Upper respiratory tract infection	0	1 (1.5)
Intervertebral disc protrusion	0	1 (1.5)
Dizziness	1 (1.6)	0
Extrapyramidal disorder	1 (1.6)	0
Hypoesthesia	1 (1.6)	0
Nephritic syndrome	1 (1.6)	0

Source: [NV-02C-004 CSR Table 14.3.1.1]

Source: 120-Day Safety Update
LdC= valtorcitabine

Medical Officer Comments: *Narrative summaries for these events were reviewed. The patient with pancreatitis in the LdT +LdC treatment arm had a number of other risks for pancreatitis, including alcohol consumption, and gallstones. Additionally, the patient with nephritic syndrome had baseline proteinuria and diabetes, which are confounding factors in this case.*

Table 142. Non-Fatal Serious Adverse Events in Study 019

Table 3-9 Summary of Serious Adverse Events other than Death in NV-02B-019 (safety population)

Event	LDT N= 122 n (%)	Lam N= 124 n (%)
Number pts reporting an AE	5 (4)	8 (6)
Myocardial infarction	2 (2)	0
Atrial fibrillation	0	1 (<1)
Cardiac arrest	0	1 (<1)
Myocarditis	0	1 (<1)
Hemorroids	2 (2)	0
Cholelithiasis	0	1 (<1)
Urinary tract infection	0	1 (<1)
Adenocarcinoma	0	1 (<1)
Syncope	0	1 (<1)
Nephrotic syndrome	0	1 (<1)
Umbilica hernia repair	1 (<1)	0

Source : [NV-02B-019 CSR Table 14.3.1.2.1.1]

Medical Officer Comments: *Narrative summaries for patients who experienced SAEs on telbivudine were reviewed. The two reports of myocardial infarction were of particular interest. The first case was that of a 52 year-old Korean male who experienced a myocardial infarction and required percutaneous stent placement while receiving telbivudine. In addition to being male and > 50 years old, this patient had known several risk factors for MI, including cigarette smoking, mild elevation of cholesterol, and family history of CAD. The second case was that of a 66 year-old Chinese male with a history of hypertension and a family history of CAD, who experienced chest pain with exertion, and was subsequently diagnosed with a myocardial infarction. This patient also had percutaneous stent placement, but subsequently experienced a cardiac arrest requiring cardioversion from which he recovered. In this reviewer's assessment, neither case of MI was likely related to telbivudine.*

Study NV-02B-011/CLDT600A2301

Table 143. **Summary of Serious Adverse Events other than death by preferred term (>1% safety population)**

Preferred term	Overall N=232 n(%)
Total number of patients	108 (46.6)
Hepatic encephalopathy	26 (11.2)
Hepatic neoplasm malignant	18 (7.8)
Peritonitis bacteria	14 (6.0)
Ascites	11 (4.7)
Pleural effusion	9 (3.9)
Gastroenteritis	6 (2.6)
Esophageal varices hemorrhage	6 (2.6)
Cellulitis	5 (2.2)
Gastrointestinal hemorrhage	5 (2.2)
Urinary tract infection	5 (2.2)
Dehydration	3 (1.3)
Encephalopathy	3 (1.3)
Hyperglycemia	3 (1.3)
Inguinal hernia	3 (1.3)
Pneumonia	3 (1.3)
Source: NV-02B-011/CLDT600A2301 Table 9-2	

Medical Officer Comments: *None of these serious adverse events are unexpected in this population with decompensated liver disease.*

Table 144. **Adverse Events leading to Treatment Discontinuation**

Table 3-11 Adverse events leading to study discontinuation in Study NV-02C-004 (Safety population)

Event	LDT N=64 n (%)	LDT+LDC N=68 n(%)	Discontinue treatment	Interrupt treatment
Hyperbilirubinemia	0	1 (1)	x	
Dizziness	1 (1.6)	0		x
Hypoaesthesia	1 (1.6)	0		x
Nephritic syndrome	1 (1.6)	0		x
Productive cough	0	1 (1)		x
pancreatitis	0	1 (1)		x
Source: [NV-02B-004 CSR Listing 16.2.7.1]				

Medical Officer Comments: *One patient in the telbivudine plus LDC arm discontinued study due to hyperbilirubinemia; while all the other adverse events listed here were for treatment interruption.*

Table 145. Adverse Events Resulting in Study Discontinuation in Study 019

Table 3-12 Adverse Events leading to study discontinuation for Study NV-02B-019 (Safety population)

Event	LDT N= 122 n (%)	Lamivudine N= 124 N (%)	Discontinue treatment	Interrupt treatment
Cardiac arrest	0	1(<1)	X	
Hepatic enzyme increased	1 (<1)	1 (<1)	X	
Adenocarcinoma	0	1 (<1)		X
Pharyngolaryngeal pain	0	1 (<1)		X
Myocarditis	0	1 (<1)		X
Fatigue	0	1 (<1)		X
Diarrhea	0	1 (<1)		X
Abdominal pain	0	1 (<1)		X
Syncope	0	1 (<1)		X
Vomiting	0	1 (<1)		X
Source: [NV-02B-019 CSR Table 14.3.1.3.1.5] and [Listing 16.2.7.1]				

Medical Officer Comments: *In this study, 1 telbivudine-treated patient discontinued telbivudine due to increased hepatic enzymes and 1 lamivudine-treated patient discontinued due to a cardiac arrest. All of the adverse events resulting in treatment interruption in this study were in the lamivudine treatment arm.*

Peripheral Neuropathy in Recently Completed and Ongoing Studies

Please refer to Table 118 in Section 7.3.4

The applicant has estimated the incidence of peripheral neuropathy as 17% when telbivudine is used in combination with pegylated interferon (pegasys) based on the preliminary safety results from study CLDT600A2406. In contrast, in the large phase 3 registrational trial (NV-02B-007), 2/680 (0.3%) LdT-treated patients experienced peripheral neuropathy, and in the overall clinical trials patients, 6 cases of peripheral neuropathy have been reported out of approximately 2000 patients treatment with LdT (0.3%). Interferon-alfa (Tunca, et al., 2004), and pegylated interferon-alfa-2a have also been associated with peripheral neuropathy (Khiani, et al., 2008;). Additionally, hepatitis B itself has been associated with peripheral neuropathy (Inoue, et al., 1987; Tsukada, 1987).

Musculoskeletal Adverse Events

The adverse events classified as musculoskeletal disorders in the recently completed or ongoing studies were summarized by the applicant by study. According to the applicant, most of these events were not considered to be related to study drug and did not lead to treatment interruption. No labeling changes regarding musculoskeletal adverse events were proposed.

Table 146. Musculoskeletal Adverse Events in Study 004

Table 3-5 Summary of Musculoskeletal events in NV-02B-004 (safety population)

	LDT N=64 n (%)	LDT+LDC N=69 n (%)
Back pain	2 (3.1)	3 (4.4)
Arthralgia	1 (1.6)	2 (2.9)
Musculoskeletal chest pain	1 (1.6)	1 (1.5)
Chondritis	0	1 (1.5)
Intervertebral disc protrusion	0	1 (1.5)
Neck pain	0	1 (1.5)
Tenosynovitis stenosans	1 (1.6)	0
Myalgia	0	1 (1.5)

Source: [NV-02B-004 Table 14.3.1.3].

***Medical Officer Comments**: More patients experienced musculoskeletal adverse events in the lamivudine group (10/69, 14.5%) than in the telbivudine treatment group (5/64, 7.8%).*

Table 147. Musculoskeletal Adverse Events in Study 019

Table 3-6 Summary of Musculoskeletal events in NV-02B-019 (safety population)

Event	LDT N=122 n(%)	Lam N=124 n (%)
Arthralgia	5 (4)	5(4)
Back pain	2 (2)	2 (2)
Myalgia	3(2)	1(<1)
Chest wall pain	1(<1)	1(<1)
Neck pain	1(<1)	1(<1)
Intervertebral disc protrusion	1(<1)	0
Limb discomfort	1(<1)	0
Musculoskeletal chest pain	1(<1)	0
Pain in extremity	1(<1)	0
Tendon disorder	0	1(<1)
Myopathy	3 (2)	1(<1)

Source: [NV-02B-019 CSR Table 14.3.1.3.1.1]

Medical Officer Comments: *The incidence of musculoskeletal adverse events in this study was higher in the telbivudine treatment arm (19/122, 15.6%) than in the lamivudine arm (12/124, 9.7%). Notably, 3 patients in the telbivudine treatment group experienced an adverse event of myopathy in this study.*

Table 148 Musculoskeletal Adverse Events in Study 011

Table 3-7 Summary of Musculoskeletal events in NV-02B-011/ CLDT600A2301 (safety population)

Event	Overall* N=232 n (%)
Arthralgia	17 (7.3)
Back Pain	17 (7.3)
Muscle cramp	13 (5.6)
Pain in Extremity	10 (4.3)
Muscle Spasms	3 (1.3)
Myalgia	7 (3.0)
Muscular weakness	2 (0.9)
Musculoskeletal chest pain	2 (0.9)
Arthropathy	1 (0.4)
Chest wall pain	1 (0.4)
Coccydynia	1 (0.4)
Groin pain	1 (0.4)
Joint swelling	1 (0.4)
Limb discomfort	1 (0.4)
Muscle Atrophy	1 (0.4)
Musculoskeletal discomfort	1 (0.4)
Musculoskeletal pain	1 (0.4)
Musculoskeletal stiffness	1 (0.4)
Myopathy	1 (0.4)
Myositis	1 (0.4)
Neck Pain	1 (0.4)
Osteoarthritis	1 (0.4)
Osteoporosis	1 (0.4)
Periarthritis	1 (0.4)
Spinal Column stenosis	1 (0.4)

* treatment remains blinded
Source: NV-02B-011/ CLDT600A2301 Table 4-2

Medical Officer Comments: *In ongoing study 011, treatment arms (telbivudine vs. lamivudine) remain blinded; however, it is notable that myopathy and myositis have also been reported in this study.*

CK Elevations (as adverse events) in recently completed and ongoing studies

No adverse events of CK elevation were reported in study NV-02C-004, NV-02B-019; and in the ongoing study NV-02B-011, 7/232 (3%) patients have experienced CK elevations reported as adverse events. However, these results remain blinded to treatment arm.

ALT flares in recently completed and ongoing studies
The AASLD definition of ALT flare (ALT elevation > 2 x baseline and > 10 x ULN) was used to identify on-treatment flares in studies 019, 011, -022, and CLDT600A2406. In study 022, 23/667 (3.4%) LdT-treated patients experienced ALT flares, 18 of these had rolled over from the 007 study, and 5 from the 015 study. Off-treatment ALT flares will be evaluated in 022; however, most patients remain on treatment at this time. ALT flares were not analyzed from study 004 for this safety update.

Pregnancy in recently completed and ongoing clinical trials
A total of 13 pregnancies which occurred during the clinical trials were reported from December 21, 2007 through April 21, 2008. Twelve of these occurred in study 022, and 1 in study 004. Nine pregnancies occurred in women treated with telbivudine, and 4 in women exposed to telbivudine via semen. Of the 9 direct exposures, 1 pregnancy ended in a missed abortion, two resulted in early termination/planned abortions, 1 resulted in delivery of low-birth weight infant, and 1 resulted in delivery of a healthy infant. No follow-up was available on the other 4 pregnancies. Of the 4 pregnancies which occurred in women exposed to telbivudine via semen, 1 pregnancy resulted in delivery via C-section; and no follow-up was available on the other 3 cases.

Postmarketing Data
No new postmarketing data was included in the 120-day safety update. The applicant referred to PSUR-3, submitted October 31, 2007.

8. Postmarketing Experience

Telbivudine was first marketed in Ghana on July 13, 2006 and in Switzerland on August 21, 2006. It is currently approved in 62 countries. The Periodic Safety Update Report (PSUR)-3, submitted on October 31, 2007, for the time period from March 1, 2007 to August 31, 2007, is reviewed in this section.

Patient Exposure
The applicant estimated cumulative patient exposure to telbivudine, based on sales data and the defined daily dose of 600 mg/day telbivudine, as 4,668 patient treatment-years. In Idenix or Novartis clinical trials, 3,614 patients had received telbivudine at the time of this report.

A total of 46 spontaneous (41) and solicited (5) cases were reported during this time period, as summarized in the following table.

Table 149. Postmarketing Adverse Events reported in PSUR-3

Table 6-1 **Overview of reported spontaneous and attributable solicited cases by report type**

	Serious		Non-serious		Total
Type of Report	Unlisted	Listed	Unlisted	Listed	
Spontaneous	6	3	17	15	41
Investigational clinical trials	4	1	0	0	5
Total	**10**	**4**	**17**	**15**	**46**

There were 10 serious unlisted reports which were described briefly by the applicant. These are summarized in the following table.

Table 150. Serious Unlisted Reports for PSUR-3 (N=10)

Number	MedDRA SOC	AE Primary (secondary)	Onset after starting LdT	Outcome	Applicant's assessment	MO assessment
PHBS2007CN13379	Blood and lymphatic system disorders	Hemolysis (decreased RBCs)	Not reported	Resolved 2 weeks after discontinuation	Unable to fully assess	Agree
PHBS2007CN12359	Cardiac disorders	myalgia, hypoaesthesia, pain, arrhythmia, cardiac discomfort; pharyngolaryngeal pain	17 days	Recovered from all events except tenderness of thigh	Information inadequate to fully assess case	Possibly related
PHBS2007CN08146	Injury, poisoning and procedural complications	Traffic accident (bradycardia)	40 days	Death (traffic accident) 3 months later	Unable to fully assess	Agree- patient had history of bradycardia;
PHBS2007CN13312	Investigations	"Decreased blood routine data"	20 days	WBC decreased to 1600/mm3; and platelets decreased to 40,000/mm3 1 month later after receiving unspecific medication	Unable to fully assess	Agree
PHHO2007TR06152	Metabolism and nutrition disorders	Hyponatremia	10 days	Resolved after treatment	Unknown	Agree- could be related to underlying cirrhosis and receipt of diuretics

PHHO2007US11998 PHHO2007FR12711 PHHO2007HK13961	Musculoskeletal and connective tissue disorders	3 reports- see section on musculoskeletal events below				
PHBS2007CN09542	Nervous system disorders	Convulsion (stiffness of limbs)	2 weeks	Unknown	Unable to fully assess	Agree
PHEH2007US05468	Respiratory, thoracic, and mediastinal disorders	Apnea post-delivery (brain damage)	2 hours post-delivery Mother received telbivudine during third trimester of pregnancy	Unchanged	Unable to fully assess	Agree- also received anti-hepB immunoglobuli and hepB vaccines within 2 hours after birth. Brain damage not confirmed

Medical Officer Comments: *Only one of the events summarized in the above table was possibly related to telbivudine in this reviewer's assessment (Case number* PHBS2007CN12359)*.However, in that cases no additional details regarding the arrhythmia or cardiac discomfort were available. This case was also reviewed in Table 152 below.*

The applicant searched for categories of events which had been identified in their risk management plan as potential safety concerns. These categories and the number of reports identified for each is shown in the following table. At the time of this PSUR there were no reports of pancreatitis, lactic acidosis, hypersensitivity or ALT flares. There were a number of musculoskeletal adverse events and CK elevations, described below.

Table 151. Results of Applicant's Search for Specific Adverse Events

AE Category	HLG or Preferred Term Search	Number of Reports
Hypersensitivity	Allergic conditions	0
Pancreatitis	Multiple PTs	0
Lactic acidosis	SMQ for lactic acidosis	0
ALT flares	ALT	0
CK elevations	Creatine phosphokinase	4
Musculoskeletal effects	SMQ for rhabdomyolysis/myopathy	8

HLG= high level group

The musculoskeletal adverse events identified in the applicant's search are described in the table below.

Table 152. Summary of Musculoskeletal Adverse Events and CK Elevation Reports from PSUR -3

Report Number	Adverse event(s)	Age and Gender	Serious	Onset	Outcome	Applicant's assessment	MO assessment
PHBS2007CN12359	"Heart discomfort", arrhythmia, tenderness/numbness of heels, muscle tenderness legs and shoulders	37 M	NR	16 days	Recovered from all events except for tenderness of the thigh	Information inadequate to fully assess case	Agree
PHBS2007CN09554	Weakness of limbs, sore waist, lower back and abdominal pain (nausea and skin rash)	F	No	"After administration of telbivudine"	Unknown; telbivudine continued		Possible-unable to assess
PHBS2007CH10276	Myalgia (elevated CK)	58 M	No	4 months	Myalgia improved CK normalized; Telbivudine continued	Medically significant	Agree
PHBS2007CN12708	Pain in right foot, hips, wrist and left shoulder	M	NR	15 days	Treated with analgesics, but worsened		Possible, but unable to assess
PHBS2007CN13693	Soreness and weakness of feet (stomach discomfort)	M	NR	Not reported	Unchanged 4 months later		Unable to assess
PHHO2007US11998	Necrotizing myopathy*	54 M	NR	2 years after starting	Telbivudine stopped; no	Probably related	Agree

	(CK elevation) Muscle weakness; sensory neuropathy			current clinical trial	resolution of events		
PHHO2007HK13961	Frequent falls; weakness of all 4 limbs (fluctuating CK levels) EMG normal; muscle biopsy-inflammatory myopathy (polymyositis)	46 M	NR	1.5 years after starting clinical trial	Telbivudine discontinued; outcome not reported	Probably related	Agree
PHHO2007FR12711	Necrotizing "toxic" myopathy** (myalgia; (elevated CK)	44 M	NR	2 years after starting clinical trial	CK levels decreased after switch to adefovir and lamivudine	Probably related	Agree

NR= not reported
*EMG showed sensory neuropathy and mild myopathic change in proximal upper and lower extremities. CK elevated since previous trial; and neuropathy since start of current trial.
**Muscle biopsy reportedly showed necrotizing myopathy (toxic) with "mitochondrial myopathy"

Medical Officer Comments: *Note that 4 of the 8 cases with musculoskeletal adverse events also had CK elevation, so there was an overlap in cases from these two AE categories.*

AERS Reports of Musculoskeletal Adverse Events with Telbivudine
A total of 28 reports of musculoskeletal adverse events were identified in the AERS database through August, 2008 in a search performed by Melissa Truffa, Safety Evaluator, Team Leader in OSE. These reports were reviewed in detail by this reviewer, and are summarized in the table. below.

Table 153. Postmarketing Musculoskeletal Adverse Events in AERS Database

Number	AERS Case Number	Patient Gender/Age	Musculoskeletal-al Adverse Event reported	Event Onset	Diagnostic tests performed and findings	Neurologic AEs also reported	CK elevation also reported	Action	Outcome	Reporters assessment of relationship to LdT	Comments
1	6335325	Male/17	Musculoskeletal stiffness	NR	NR	convulsion	NR	Treated with calcium-no effect	NR		Prior interferon
2	6367520	Male/54 Study -022	Myopathy	Within month	NR	none	NR	Discontinued	Continuing	related	NR
3	638332	Male/37	Myalgia, cardiac discomfort	Within month	NR	hypoesthesia	NR	Discontinued	Continuing	Related	Muscle tenderness legs shoulders, heels; Arrhythmia also reported as AE
4	6445934	Female/unk	Muscle weakness	NR	NR	somnolence	NR	discontinued	Unknown	Not related	Considered secondary to hyper-thyroidism
5	6461308	Unk/unk	Pain in extremity; increased CK	NR	NR	NR	yes	NR	NR	NR	Concomitant interferon
6	6463739	Male/unk	Myalgia; increased CK	NR	NR	Peripheral neuropathy	Yes: 5632 IU/L (170 ULN)	NR	NR	NR	Possible concurrent interferon
7	6517038	Male/unk (Study 2406)	Myositis, myalgia; increased CK		EMG-incipient mild poly-neuro-pathy LEs; NCS abnormal	Peripheral sensory neuropathy, paraesthesia	yes	NR	disability	Probably related	Telbivudine plus Pegasys
8	6517039 *	Male/32	Mitochondrial myopathy, muscle	Muscle biopsy: inflammator			yes-5631	LdT and Pegasys discontinued			Possible concurrent interferon

			necrosis, myalgia, myopathy	y myopathy with necrosis and mitochondrial myopathy; EMG:normal							
9	6522629	Male/unk (Study -022)	Myopathy, increased CK, myositis, muscular weakness; intervertebral disc disorder	6 months	NCS- mild to mod. Axonal peripheral neuropathy	Neuropathy, peripheral;	Yes 1148	discontinued	recovered	Muscle weakness related	Myopathy not confirmed by biopsy
10	6548119	Male/20	Pain in extremity, arthralgia, increased CK			Hypoaesthesia	Yes 1664	discontinued			Also received peg-interferon
11	6549998	Male/20	Pain in extremity, myalgia,	1.5 years		peripheral neuropathy, hypoaesthesia	yes	discontinued	ongoing		Appears to be same pt. as 6548119
12	6552818	Unk/unk	Myalgia, increased CK				Yes: 900 IU/L	discontinued	NR	suspected	
13	6567952	Male/56 (Study -022)	Muscle atrophy, myopathy, polymyositis, muscular weakness, myalgia, limb discomfort, musculoskeletal pain	5-6 months	EMG-NCS: mild sensory-motor poly-neuropathy with demyelination; muscle biopsy: mild inflammatory infiltration, and scattered atrophic muscle fibers	Demyelinating poly-neuropathy, hypoaesthesia, impaired hearing	Yes: 1340	none	unchanged	related	
14	6569064	Male/unkno	Musculoskelet	2 weeks			Yes: 3200	discontinued	recovered	probable	Pt. had

		wn	al discomfort, increased CK; rhabdomyolysis								ESRD on hemo-dialysis at baseline; myoglobin not reported; rhabdo not confirmed
15	6585992	Unk/unk	Myalgia, abasia	5 months			CK: 200	Discontinued	NR	related	Difficulty walking; also received Peg-interferon
16	6637865	Male/40	Asthenia, myalgia, CK increased	NR		Hypoaesthesia; neuralgia	yes	NR	NR	NR	
17	6643206 (Study -022)	Male/44	Myalgia, pain, mitochondrial myopathy, muscle necrosis, CK increased		Muscle biopsy: necrotizing (toxic) myopathy with mitochondrial myopathy		Yes: 2910 IU/L	discontinued	improved	related	
18	6675633	Male/20	Pain in extremity, CK increased; Gait disturbance	6 months?	NR		Yes: 1310	discontinued	NR	NR	LdT added to Pegasys. Myoglobin increased (738.2 µg/L ref. 0-70 µg/L)**; smooth muscle Ab-positive; histone AB-positive
19	6704687	Male/45	Muscular weakness, musculoskelet	15 months	NR	Hypoaesthesia, neuralgia	Yes: 438 IU/L	Reduced dose LdT from 600 mg bid to qd;	improved	NR	Literature report ()

			al pain, myalgia, myopathy; CK increased					adefovir added			
20	6704690	Male/37	Muscular weakness, myalgia; CK increased	2 weeks		Hypoaesthesia, neuralgia	Yes: 191 IU/L	LdT Discontinued	Improved	NR	Literature report () Concomitant interferon
21	6704698	Male/30	Muscular weakness, myalgia; CK increased			Hypoaesthesia, neuralgia	Yes: 311 IU/L	LdT Discontinued	Improved	NR	Literature report () Concomitant interferon
22	6704709	Male/25	Asthenia, myalgia, CK increased	1 month		Hypoaesthesia, neuralgia	Yes: 425 IU/L	LdT Discontinued	Improved	NR	Literature report () Concomitant interferon
23	6704711	Male/35	Muscular weakness, myalgia, CK increased	5 months		Hypoaesthesia, neuralgia	Yes: 900 IU/L	LdT discontinued	Some improvement	NR	Concomitant adefovir
24	6722549	Unk/unk	Myocarditis, CK increased; CK-MB increased				Yes: CK: 900; CK-MB: 180 (90 ULN)	LdT discontinued	NR	LdT suspected	LdT added to interferon x 3 months; then LdT alone x 6 months
25	6723282	Unk/unk	CK increased; CK-MB increased	1-2 months			Yes: CK >4000; CK-MB: 400	NR	Death (lactic acidosis)	NR	Concomitant adefovir;
26	6723938	Unk/25	CK increased; CK-MB increased				CK 1332 IU/L; CK-MB 66.6 IU/L	LdT discontinued	Death (multi-organ failure)	suspected	Liver and renal failure; urine occult blood-positive; metabolic acidosis***
27	6730128	Female/45 (Study-022)	Asthenia, malaise,	2 months	EMG consistent with	Peripheral neuropathy	NR	LdT discontinued	continuing	possible	AEs post-pneumonia

			myopathy		myopathy LEs and thoracic paraspinals with muscle fiber irritability						
28	6730128	Male/25	Myalgia, CK increased; rhabdomyolysis	1.5 months			Yes: 3800	LdT discontinued	Improved	probably	Baseline ESRD on dialysis; also developed hyperkalemia; increased BUN

Unk= unknown; LE= lower extremities
*possible duplicate of case number 6463739.
** possible case of rhabdomyolysis, but not reported as such
***description of case sounds like lactic acidosis, but lactic acid level not reported; rhabdomyolysis with renal failure also possible, but urine or serum myoglobin not reported.

Medical Officer Comments: *At least 2 of these cases were duplicate reports regarding the same patient. From these AERS reports, a number of significant musculoskeletal adverse events, including myopathy, myositis, and others were reported in association with telbivudine use. At least one case (6675633) was associated with increased myoglobin (unknown if urine or serum myoglobin) suggesting that rhabdomyolysis may have been present; and in one other case (6723938), based on review of the narrative, rhabdomyolysis may have been present, but was not reported as such. Rhabdomyolysis was reported in case 6730128 in a patient with baseline ESRD on dialysis who developed CK elevations and worsening renal failure, making interpretation of the case difficult. Many of these events were associated with CK elevation, and some had associated neurologic signs/symptoms consistent with peripheral neuropathy. A number of these cases were associated with concurrent use of interferon, as seen in a number of cases of peripheral neuropathy reported in a study which evaluated telbivudine monotherapy vs. telbivudine in combination with pegylated interferon, as discussed below. Note that 5 of these cases were from a literature report (Zhang, et al., 2008) which retrospectively reviewed adverse reactions in 105 patients treated with telbivudine for hepatitis B. In 4/5 cases reports the term "arrhythmia" was also used to describe an adverse event, but no further details were provided. At least one case of myocarditis, associated with CK-MB elevation, was reported to AERS, but case details were scanty. Although the term myocarditis was not found upon search of the clinical trials safety database (pooled studies NV-02B-007 and -015), it seems feasible that telbivudine could affect cardiac muscle as well as skeletal muscle. In some cases of CK elevation, CK-MB elevation was also noted. The mechanism of muscle toxicity has not been elucidated, but at least two cases here reports adverse events of mitochondrial myopathy or toxicity based on muscle biopsy.*

An additional spontaneous case report of rhabdomyolysis was submitted to AERS on October 1, 2008. This male patient (age not provided) was treated with telbivudine for approximately 2 years prior to the initial adverse event reported by the physician on September 26, 2008, with follow-up reports on September 27 and 28, 2008. Two months prior to the AE report, the patient had experienced pain in arms and chest, but attributed it to playing basketball, and used an analgesic for pain. The muscular pain continued and worsened, and became a generalized body ache. One week prior to the AERS report, the patient was seen by a physician and was found to have an elevated CK (1200 IU/L) and mild elevation of CK-MB (value not reported). The patient was hospitalized for a cardiac workup which was subsequently found to be negative. One day prior to the AERS report, the patient experienced sudden dyspnea and lassitude. He was hospitalized (ICU) and found to have severe circulatory collapse, and multiple organ failure with hypotension, increased creatinine, BUN, "hyperlacticacidemia", increased ALT and AST (each over 300 IU/L), and he became anuric and icteric. Plasma myoglobin was increased, and CK-MB increased to > 50 IU/L. The patient was treated with vasopressors, glucocorticoids, "medications for acidosis", and hemodialysis. Telbivudine was discontinued on the day the case was initially reported to AERS. Entecavir was subsequently started and the patient's condition improved.

Medical Officer Comments: *This latter case is clearly consistent with rhabdomyolysis, with elevated CK, renal failure, and elevated blood myoglobin. No other medications associated with rhabdomyolysis were reported. Lactic acidosis may have also contributed to the patient's*

symptoms and multiple organ failure. A relationship to telbivudine is suspected, particularly with the positive de-challenge observed in this case. We propose to include rhabdomyolysis and lactic acidosis in the Postmarketing Adverse Events section of the final product labeling.

Peripheral Neuropathy

A search for peripheral neuropathy was also undertaken using the broad SMQ "peripheral neuropathy". Two cases of peripheral neuropathy were identified. Both of cases were also listed under musculoskeletal adverse events, including the 37 year-old male with "heart discomfort", arrhythmia, tenderness and numbness of the heels, and muscle tenderness of the legs (number PHBS2007CN12359); and the 54 year-old male with necrotizing myopathy, neuropathy, and CK elevation (number PHHO2007US11998 and PHHO2007US11998), described in Table 152 above.

Medical Officer Comments: *Although the mechanism(s) of the neuropathy and myopathy associated with telbivudine use have not been elucidated; like that observed with other nucleoside analogues, mitochondrial toxicity is suspected. In vitro studies submitted by the applicant revealed no evidence for mitochondrial toxicity with this drug; however, in vitro effects may not always reflect in vivo toxicity.*

After the end of the reporting period for this PSUR, the applicant received 4 additional reports of peripheral neuropathy, and provided a brief description of these cases, which are summarized in the table below.

Table 154. Preliminary description of Additional Reports of Peripheral Neuropathy

Report Number	Adverse event or symptoms	Age and gender	HBV Treatment	Onset after starting telbivudine	Outcome	Applicant's assessment	Reviewer's assessment
PHHO2007IL15386*	Polyneuropathy	21 M (on A2406 study)	Telbivudine + Pegasys	67 days	Study medication temporarily interrupted; improved	suspected	Possible
PHHO2007IL15855*	Bilateral leg pain (EMG showed bilateral sensory neuropathy)	24 F (on A2406 study)	Telbivudine + pegasys	128	Study medication permanently discontinued; improved	suspected	possible
PHBS2007CN14416	Symmetric numbness, tenderness, paraesthesia (ankles) diagnosed as peripheral neuritis	28 M	Telbivudine	4 months	Not reported	Not assessed	Possible
PHBS2007IN14433	Numbness and burning both feet and polyarthralgia	31 M	Telbivudine	Unknown	Treated with gabapentin-improved; no drug discontinuation	Not assessed	Unable to assess (report of underlying neuropathic pain)

* Additional information on these cases was provided by the sponsor on September 22, 2008 by FDA request.

The Division requested a consultation from OSE to assess telbivudine postmarketing reports in the AERS database. Please refer to Melissa Truffa's consultation report. AERS reports of peripheral neuropathy are reviewed below.

Postmarketing Adverse Event Reports of Peripheral Neuropathy

A review of the AERS database for adverse event reports of peripheral neuropathy was performed by Melissa Truffa, Safety Evaluator Team Leader in OSE. A total of 29 AERS reports of peripheral neuropathy were identified. Of these 29 cases, 16 (55%) had received concomitant interferon; 12 (41%) had received telbivudine monotherapy for hepatitis B, and in one case the reporter thought that maybe the patient had also received interferon therapy. Eleven patients were from clinical trials (studies A2406 - 7 cases; and 022 - 4 cases). The median age for all cases was 38 years (range 20 to 68 years); and median time to onset overall was 6 months (range 1.5 to 23 months). However, among patients treated concomitantly with interferon, the median time to onset of peripheral neuropathy symptoms was 6 months; while among patients who received telbivudine alone, median time to onset was 10 months. These cases are described in the following tables. Note that some of the cases described here were described above in the applicant's 120-Day Safety Update and/or PSUR-3 reviewed above.Table 155. AERS Reports of Peripheral Neuropathy with Telbivudine monotherapy for Chronic Hepatitis B

Number	AERS Case Number	Patient Gender/Age	Adverse Event reported	Event Onset	Diagnostic tests performed and findings	Musculoskeletal AEs also reported	CK elevation also reported	Action	Outcome	Comments
1	6463739	Male/Unknown	Peripheral neuropathy	2 months	No	Myalgia	CK 5631	LdT discontinued	OT	Physician stated that patient might be taking interferon concomitantly.
2	6522629	Male/64 (study -022)	Peripheral neuropathy	20 months	NCS: mild to mod. axonal peripheral neuropathy; EMG: no denervation or myopatonic features	Myopathy, intervertebral disc disorder, muscular weakness, myositis	CK 1148	unknown	OT	Lumbar disc disease might be confounding event.
3	6455769	Female/30	Hypoesthesia, limb discomfort, peripheral neuropathy	unknown	EMG: damage to peripheral nerves of both legs, especially sensory nerves	Not reported	Not reported	Unknown	OT	--

4	6567952	Male/56 (study-022)	Demyelinating polyneuropathy, Hypoaesthesia	16 months	EMG and NCV showed mild sensory-motor polyneuropathy with predominant features of demyelination; muscle biopsy: "atrophic muscles fibers scattered around"	Muscle atrophy, myopathy, polymyositis, muscular weakness, myalgia, limb discomfort, musculoskeletal pain	CK 1340		HO	
5	6629222	Male/63 Study -022	Peripheral neuropathy, polyneuropathy, hypoaesthesia, paraesthesia	21 months	Neuro exam: diffuse sensory motor polyneuropathy	None reported	CK 1765	unknown	OT	CK elevated (CK 1000) prior to entering study
6	6646620	Male/22	Gait disturbance, pain in extremity, skin burning sensation, areflexia, ataxia, balance disorder, hypoesthesia, neuralgia, paraesthesia, polyneuropathy	2 months	NCS: abnormal; gastrocnemius nerve conduction absent; neuro exam: hypoaesthesia below both knees	Muscle spasms, muscular weakness,	CK 105	LdT continued; treated with traditional Chinese medications and mouse nerve growth factor; and condition unchanged	OT	Prior interferon for 3 months before switch to LdT
7	6646621	Male/unknown	Hypoaesthesia, neuralgia, peripheral neuropathy, EMG abnormal	2 months	EMG: peripheral neuropathy	No	Not reported	Treated with peripheral nerve nutritional meds; recovered	OT	Prior interferon for 3 months; switched to LdT
8	6646624	Male/unknown	Hypoesthesia, pain in	2 months	Not reported	no	Not reported	Not reported	OT	Prior interferon for

			extremity; headache							2 months; switched to LdT
9	6687163	Male/unknown	Abasia, peripheral neuropathy	6 months	Not reported	Not reported	Not reported;	LdT discontinued; outcome unknown	OT	
10	6687560	Male/40 Study A2406	Hypoaesthesia, radiculopathy	9 months	NCS: no evidence of peripheral neuropathy	Not reported	Not reported	Not reported	OT	Had not received Pegasys
11	6691985	Female/68 Study -022	Hypoaesthesia, polyneuropathy	23 months	EMG: lower limb sensory polyneuropathy	Not reported	Not reported	Not reported	OT	
12	6725590	Male/32 BMS clinical trial	Hypoaesthesia	2 months	Not reported	Not reported	Not reported	LdT discontinued; event ongoing 4 months after discontinuation	OT	
13	6727011	Male/unknown	Hypoaesthesia, peripheral neuropathy	7.5 months	Not reported	Not reported	CK increased	Switched from LdT to Lam; improved	OT	

Suspect 664620, 664621 and 664624 may be reports from same patient, who had received prior interferon therapy for HBV.
NCV= nerve conduction velocity; NCS= nerve conduction study; EMG = electromyogram

Table 156. AERS Reports of Peripheral Neuropathy with Telbivudine and Interferon treatment for Chronic Hepatitis B

Number	AERS Case Number	Patient Gender/Age	Interferon received	Neurologic Adverse Event(s) reported	Event Onset	Diagnostic test(s) and findings	Musculoskeletal AEs also reported	CK elevation also reported	Action	Outcome	Comments
1	6426997	Male/21 Study A2406	Pegasys	Peripheral sensory neuropathy, sensory loss, pain, paresthesia	3 months	NCV: axonal sensory motor polyneuropathy; EMG: axonal sensory motor polyneuropathy	None reported	No: CK 115	Pegasys and LdT stopped; improved	HO	--
2	6434755	Female/24 A2406	Pegasys	Peripheral sensory neuropathy	4 months	EMG: bilateral sensory neuropathy	None reported	Not reported	Pegasys and LdT stopped; lamivudine started; symptoms unchanged	OT	
3	6455774	Male/23	Pegasys	Hyperaesthesia, hypoaesthesia, pain in extremity, nerve injury	4 months	EMG: damage to both motor and sensory nerves		CK 1668; CK-MB increased : 49.2 U/L (normal range 0-24 U/L)	Pegasys and LdT stopped; lamivudine, B1 and B12 started	OT	
4	6461308	Unknown gender and age	Interferon	Pain in extremity	6 months	Not reported	None reported	CK increased;	Not reported	HO	--
5	6517038 Study A2406	Male/47	Pegasys	Peripheral sensory neuropathy, paresthesia	3 months	NCS: abnormal, lower limb evoked potential of low amplitude; initial EMG normal, subsequent	Myositis, myalgia	CK increased; CK 2189	Pegasys and LdT stopped; improved, but persistent mod. Disability	DS	

						EMG showed mild distal and symmetric polyneuropathy of 4 limbs without denervation; later EMG showed distal symmetric polyneuropathy sensorimotor that was predominantly axonal.					
6	6534845 Study A2406	Male/55	Pegasys	Peripheral neuropathy; demyelinating polyneuropathy, hyperaesthesia, paraesthesia	6 months	EMG: demyelinating incipient motor sensitive polyneuropathy	None reported	Not reported	Pegasys and LdT stopped; improved	OT	
7	6549998	Male/20	Interferon	Hypoaesthesia, peripheral neuropathy, pain in extremity	6 months	Neurologist diagnosed peripheral neuritis	myalgia	CK increased; CK > 1000	Interferon and LdT stopped; adefovir started; persistent symptoms 6 months later	HO	
8	6652090 Study A2406	Male/33	Pegasys	Hypoaesthesia, peripheral sensory neuropathy, carpal tunnel syndrome, radiculopathy	4 months	NCV: early stages of polyneuropathy, predominantly sensori-motor axonal degeneration	Myalgia	Not reported	LdT had been stopped 1 month prior to symptom onset; Pegasys stopped 1 month after	OT	Also had herniated intervertebral disc, which may be confounding factor.

									symptoms started		
9	6586893	Male/38	Pegasys	polyneuropathy	1.5 months	NCV: early stages polyneuropathy, predominantly sensori-motor axonal degeneration	Not reported	Not reported	LdT stopped; not recovered	OT	
10	6608787 A2406	Female/24	Pegasys	Peripheral neuropathy, pain, hypoaesthesia, paraesthesia, burning sensation, vibration test abnormal	2.5 months	EMG: mild sensory peripheral neuropathy, predominantly axonal	Muscle spasms	Not reported	Tenofovir started; symptoms still causing significant disability	OT	
11	6651379	Male/40	interferon	Gait disturbance, hypoaesthesia	6 months	Not reported	None reported	Not reported	LdT stopped, interferon continued; no improvement	OT	
12	6653419	Male/42	Pegasys	Peripheral nerve biopsy, demyelination, nerve degeneration, paraesthesia, peripheral sensory neuropathy	7 months (1 month after starting Pegasys)	NCS: sensory neuropathy, nerve biopsy right sural nerve: active axonal degeneration and myelin breakdown	None reported	Not reported	Not reported	HO	Also on adefovir??
13	6672341	Female 25	Interferon-alpha-2b	Anaesthesia, dysaesthesia, hypoaesthesia, paraesthesia	3 months	Not reported	Muscular weakness	Not reported	LdT stopped; condition unchanged	OT	
14	6673239	Male/26	interferon	Peripheral neuropathy, pain in	2.5 months	Not reported	None reported	Not reported	unchanged	OT	

				extremity							
15	6701539	Male/38	Pegasys	Peripheral neuropathy	6 months	Unspecified test: normal	None reported	Not reported	LdT and Pegasys discontinued	OT	On LdT 3.5 months before adding Pegasys
16	6710124	Female/39	Pegasys	Gait disturbance, polyneuropathy,	11 months	Not reported	None reported	Not reported	LdT stopped; entecavir started; unknown if Pegasys stopped permanently	OT	

Medical Officer Comments: *Peripheral neuropathy, in many cases confirmed by nerve conduction studies or EMG, was reported in patients treated with telbivudine alone and in those who received telbivudine plus an interferon. Although it is difficult to assess severity from the postmarketing reports, in both settings (with or without interferon), peripheral neuropathy was associated in some cases with significant disability (inability to walk, etc...), and was sometimes associated with CK elevation and/or muscle weakness, myalgia or myopathy. The onset of peripheral neuropathy symptoms may be more rapid and possibly more severe in patients treated with telbivudine plus an interferon than in those who received telbivudine alone. Interferons have been associated with peripheral neuropathy rarely (Tunca, 2004; Khiani, 2008). Hepatitis B itself has been associated with peripheral neuropathy (Inoue, 1987; Tsukuda, 1987). In a number of these cases, the peripheral neuropathy was also associated with musculoskeletal adverse events and/or CK elevation. This may suggest a common mechanism for neuropathy and myopathy associated with telbivudine (e.g. mitochondrial toxicity*

Peripheral Neuropathy with Other Approved Drugs for Treatment of Chronic HBV
Although peripheral neuropathy has been identified as a significant safety concern with some of the nucleoside analogues used to treat HIV, particularly ddC, ddI, and d4T, peripheral neuropathy has not been identified as a safety issue for any of the nucleosides/nucleotides approved for treatment of HBV to date. Melissa Truffa, Safety Evaluator, Team Leader, OSE, searched the AERS database on Sept 4, 2008 for adverse events reported under the SMQ for peripheral neuropathy for approved anti-HBV drugs, with the exception of tenofovir which was approved recently for HBV (August 11, 2008).

The following table summarizes the number of AERS postmarketing adverse event reports identified by this search. A Trade Name search for Epivir HBV was performed rather than for lamivudine, because lamivudine is also used in combination with other antiretroviral agents for treatment of HIV a search on lamivudine would be significantly confounded due to the concomitant or prior use of other antiretrovirals associated with peripheral neuropathy.

Table 157. AERS Post-marketing reports peripheral neuropathy with other nucleosides/nucleotides approved in the US for HBV treatment

Approved drug for Treatment of HBV	Approval Date	Number of Crude AERS Reports
Epivir HBV (lamivudine)	December 8, 1998	2
Adefovir	September 20, 2002	12
Entecavir	March 29, 2005	1
Telbivudine	October 25, 2006	29

The reports for EpivirHBV, adefovir and entecavir were reviewed to determine if there was any clear relationship between the adverse event(s). The telbivudine cases were reviewed above. The following table summarizes the AERS reports of peripheral neuropathy for adefovir, epivir HBV and entecavir. Of the 12 adefovir reports, two did not actually describe a peripheral neuropathy, and were not included in the table below. Additionally, there were three duplicate reports found for adefovir, resulting in a total of 7 adefovir cases.

Table 158. AERS Reports of Peripheral Neuropathy with other HBV nucleosides/nucleotides

HBV Treatment	Mfr. Report Number	Gender/Age	Adverse Event(s)	Reporter's Assessment of Relationship	MO assessment of Relationship	Comments
Epivir HBV	A0108110A	Female/44	Neuropathy right lower extremity	Not reported	Insufficient information	
Epivir HBV	A0146492A	Male/52	Neuropathy in legs and feet*	Not reported	Insufficient information	HIV-negative
Entecavir	13900410	Not reported	Neuropathy	Not reported	Insufficient information	
Adefovir	HK-Gilead-E2B_00000146 and HK-Roche-566326	Male/42	Axonal neuropathy, paraesthesia	Not reported	Confounded due to concomitant medications	Treated with adefovir + LdT for 6 months, then Pegasys for 3-4 months
Adefovir	2004-0007712	Male/unknown	Peripheral neuropathy	Not reported	Insufficient information	No concomitant medications
Adefovir	B0303235A	Male/47 (literature report)	Peripheral neuropathy	Not reported	Not related	Patient with HIV/AIDS had peripheral neuropathy considered secondary to stavudine prior to starting adefovir. Hydroxyurea with antiretrovirals also associated with peripheral neuropathy
Adefovir	A0116684A	Male/42	Peripheral neuropathy, permanent nerve damage in toes, difficulty walking	Not related	Confounded due to concomitant medications	Pt. with HIV, concurrent medications included lamivudine, acyclovir, indinavir, terbinafine, and hydroxyurea; prior stavudine, combivir, abacavir, and amprenavir
Adefovir	2004-0006914	Female/44 (enrolled in study GS-01-554)	Severe foot pain ? peripheral neuropathy	Not related	Insufficient information	Pt had cirrhosis, hypothyroidism (which may be associated with

						myalgias or arthralgias)
Adefovir	US-Gilead-2003-06021	Male/41	Peripheral neuropathy (worsening)		Possible, but confounded due to concomitant medications	HIV-co-infected; history of peripheral neuropathy, concurrent abacavir, lamivudine, zidovudine, amprenavir, acyclovir, and others
Adefovir	JP-Gilead-2007-0013768 and B0489997A	Male/58	Ataxia, coordination abnormal, hyporeflexia, polyneuropathy, muscle weakness, hypoaesthesia, diplopia, Miller-Fisher syndrome	Possibly related	Possibly related, but confounded (concurrent lamivudine)	Lamivudine, amlodipine concurrent

*Consumer reported, and event described as wasting of the arms and legs, and associated with increased abdominal girth, and breast enlargement, and may not have been peripheral neuropathy.

Medical Officer Comments: *None of these cases are compelling for an association between Epivir HBV (lamivudine), entecavir, or adefovir and peripheral neuropathy, due to insufficient information, or due to confounding factors (antiretroviral therapy, or other concomitant medications). Many of these patients were co-infected with HIV and had other risk factors for peripheral neuropathy. In one adefovir case, the patient was treated with telbivudine and adefovir at the same time, and pegylated interferon-alfa-2a was added 3 months later. In this case, peripheral neuropathy was documented by nerve conduction studies which showed evidence of sensory neuropathy, and sural nerve biopsy which showed active axonal degeneration. However, the timing of the adverse event relative to initiation of telbivudine and adefovir or pegylated interferon-alfa-2a was not reported. Based on the available current postmarketing information, it does not appear that peripheral neuropathy is a major class-effect of nucleosides or nucleotides approved for treatment of HBV.*

Hepatitis Flares

Two cases of "hepatitis flare-ups" were reported during the reporting period for PSUR-3. The first was in a male patient taking Sebivo 600 mg for CHB for 22 days; with increased transaminases. After 3 months of treatment, transaminases continued to increase, and HBV viral load remained elevated, and the drug was considered to be ineffective. The second case was that of a 31 year-old male who received telbivudine in the open-label study, NV-02B-022, after completing study NV-02B-007, 015, or 018. Treatment had not been interrupted. The event was

considered related to study drug due to lack of efficacy or emergence of resistant virus. The event resolved after telbivudine was discontinued.

No reports of ALT or hepatitis flares were identified in the AERS database in a search through August, 2008.

Other Postmarketing Adverse Events Reported in AERS

Melissa Truffa, Safety Evaluator Team Leader, for OSE, performed detailed analysis of postmarketing adverse events reported to AERS. In brief, a total of 98 AERS reports for telbivudine were identified through August, 2008, 14 of these were U.S. cases; and 61 were from outside the U.S. The median patient age was 38 years (ranging from 12-63 years). Twenty six reports were in females and 61 in males.

Datamining analysis revealed a potential safety signal (EB05 $\geq$ 2) for the following adverse events: arrhythmia, increased AST, increased blood CK, myalgia, muscular weakness, pain in extremity, neuralgia, hypoaesthesia, peripheral neuropathy, and drug exposure during pregnancy, as shown in the following table.

Table 159. Data Mining Results for Telbivudine (through Aug 2008) Organized by System Organ Class (SOC)

Ingredient	PT	N	EB05	EBGM	EB95	SOC
Telbivudine	Arrhythmia	6	2.713	8.987	30.249	Card
Telbivudine	Aspartate aminotransferase increased	7	2.172	4.243	8.356	Hepat
Telbivudine	Alanine aminotransferase increased	4	1.026	2.344	4.768	Hepat
Telbivudine	Blood creatine phosphokinase increased	18	22.339	33.601	48.95	Musc
Telbivudine	Myalgia	15	7.163	14.304	23.128	Musc
Telbivudine	Muscular weakness	9	4.076	11.278	25.459	Musc
Telbivudine	Pain in extremity	8	2.272	4.199	7.554	Musc
Telbivudine	Myopathy	3	1.256	5.246	47.203	Musc
Telbivudine	Neuralgia	7	28.82	57.147	104.164	Nerv
Telbivudine	Hypoaesthesia	18	15.839	23.871	34.808	Nerv
Telbivudine	Neuropathy peripheral	6	2.471	6.896	24.581	Nerv
Telbivudine	Polyneuropathy	4	2.298	16.314	66.975	Nerv
Telbivudine	Paraesthesia	5	1.272	2.68	5.139	Nerv
Telbivudine	Gait disturbance	4	1.126	2.58	5.28	Genrl
Telbivudine	Drug exposure during pregnancy	10	2.435	4.184	6.924	Preg
Telbivudine	Caesarean section	3	1.097	3.117	12.756	Preg

Postmarketing musculoskeletal adverse events and peripheral neuropathy, and symptoms, thereof, were reviewed above. CK elevation is a known safety issue for telbivudine. AERS was also searched for other adverse events of interest, including lactic acidosis, and pancreatitis, renal impairment, and arrhythmia. There were two reports of lactic acidosis with telbivudine, one report of renal impairment with proteinuria. No further information was available for the case of renal impairment with proteinuria.

There were 10 AERS reports of telbivudine pregnancy exposure in AERS. No details were available for 2 cases, a normal delivery was reported in 5, an elective termination in 1, intrauterine death at 40 days in 1, apnea with cystic lesion in brain and cerebral edema in utero in 1 case. The latter case was reviewed in Section 7.6.2 above.

Medical Officer Comments: *Because of the pregnancy registry for telbivudine, cases of telbivudine exposure would be automatically reported to AERS. However, reporting to the APR is voluntary and captures only a small percentage of pregnancies.*

Five cases of arrhythmia were identified in AERS. Four of these were from the same literature report (Zhang, et al., 2008). In that publication the author describes 5 cases of musculoskeletal and/or neuropathic adverse events among 105 outpatients treated with telbivudine. Arrhythmia was reported in only one of those cases, and was not further described. One other case of arrhythmia was reported by a physician to AERS. This patient had been treated with telbivudine for an unspecified length of time and experienced CK elevation (CK 900 IU/L), with "myodynia" and "anisorythmia." No further details were provided.

Medical Officer Comments: *It appears that there were only two unique reports of arrhythmia in AERS, and that 3 cases were reported in error. Insufficient detail for these reports was provided to determine whether these events might be related to telbivudine.*

The case of pancreatitis was reported in a patient who initially enrolled in Study NV-02B-007 and randomized to either telbivudine or lamivudine, and subsequently enrolled in study NV-02B-022. The patient was hospitalized with acute pancreatitis approximately 3 months after starting telbivudine. This case was confounded, however, by the concomitant receipt of adefovir, and the presence of a pancreas divisum, and a clear relationship to telbivudine cannot be established. Pancreatitis resolved spontaneously without stopping either telbivudine or adefovir.

The cases of lactic acidosis are reviewed below:

AERS Case Number 6730125: This was a consumer report of lactic acidosis was in a 23 year old male treated with telbivudine and interferon, requiring hospitalization. Outcome was not reported.

AERS Case Number 6723282: This was a physician report of a patient (age and gender not reported) treated with telbivudine and adefovir for chronic hepatitis B. Approximately 2 months after starting these medications, the patient was found to have a bicarbonate level of 14, blood pH of 6.7, elevated CK (> 4000) and CK MB (400), elevated WBC 25,000, and elevated lactic acid (laboratory value not provided). This patient required ICU admission, and subsequently died (date not reported). The patient had reportedly experienced an URI one week prior to this event from which he/she recovered.

Medical Officer Comments: *The approved Tyzeka label carries a Boxed Warning for lactic acidosis. This is a class warning for all nucleosides/nucleotides approved for the treatment of HIV and hepatitis B virus. Lactic acidosis was not reported with telbivudine in the clinical studies, and these are the first post-marketing reports for this adverse event.*

In a literature search to August 31, 2007, the applicant identified no publications which contained new contained new safety findings relative to telbivudine. In a PubMed search by this reviewer conducted September 8, 2008, two publications were identified which contained some information relevant to telbivudine safety. These are listed and summarized below:

1. Zhang, et al. 2008. World J. Gastroenterology 2008; 14: 3549-3553. This publication describes 5 patients with "serious" AEs associated with telbivudine in an observational study of 105 outpatients. (3 had concurrent treatment with IFN, 1 with adefovir). Myalgia accompanied by generalized weakness was the most common adverse event (5 patients), followed by numbness (4 patients), neuralgia (1 patient), and cardiac arrhythmia (1 patient). CK was elevated in all cases with adverse events. Cardiac arrhythmia was reported in one patient, although the arrhythmia was not further described. These cases were described in Section 8 Postmarketing Adverse Events.
2. Bridges, et al. 2008. AAC 2008; 52:2521-2528. This publication described the nonclinical safety profile of telbivudine. Axonopathic findings in 9-month monkey study-monkeys dosed at 1,000 mg/kg/day (sciatic nerve and spinal cord) were described, but the findings were considered equivocal.

9 Appendices

9.1 References:

Bridges EG, Selden JR, and Luo S. Nonclinical safety profile of telbivudine, a novel potent antiviral agent for treatment of hepatitis B. Antimicrobial Agents Chemotherapy 2008; 52: 2521-2528.

Dienstag JL. Hepatitis B virus infection. N Engl J Med. 2008; 359:1486-1500.

Fodale V, Mazzeo A, Pratico C, Aguennouz M, Toscano A, Santamaria LB, and Vita G. Fatal exacerbation of peripheral neuropathy during lamivudine therapy: evidence for iatrogenic mitochondrial damage. Anaesthesia 2005; 60:806-810.

Inoue A, Tsukada M, Koh C-S, Yanagisawa N. Chronic relapsing demyelinating polyneuropathy associated with hepatitis B infection. Neurology 1987; 37:1663-1666.

Khiani V, Kelly T, Shibli A, Jensen D, Mohanty SR. Acute inflammatory demyelinating polyneuropathy associated with pegylated interferon alfa-2a therapy for chronic hepatitis C infection. World J Gastroenterol. 2008; 14:318-321.

Lau DT-Y and Bleibel W. Review: Current status of antiviral therapy for hepatitis B. Ther Adv Gastroenterol. 2008; 1:61-75.

Lok ASF and McMahon BJ. Chronic hepatitis B. Hepatology 2007; 45:507-539.

Palumbo E. Hepatitis B genotypes and response to antiviral therapy. Am J Ther. 2007; 306

Tsukada N, Koh C-S, Inoue A, and Yanagisawa N. Demyelinating neuropathy associated with hepatitis B virus infection. J. Neurol. Sci 1987; 77:203-216.

Tunca A, Erbaykak M, and Turkay C. Axonal neuropathy and hearing loss associated with alpha interferon treatment in chronic hepatitis B: A case report. Turk J Gastroenterol. 2004; 15:97-99.

Zhang X-S, Jin R, Zhang S-B, and Tao M-L. Clinical features of adverse reactions associated with telbivudine. World J Gastroenterol. 2008; 14:3549-3553.

9.2 Labeling Recommendations

The applicant has proposed the following update to the telbivudine label:

Under the label heading **WARNINGS AND PRECAUTIONS:**

[redacted] b(4)

Under the label heading **CLINICAL PHARMACOLOGY Drug Interactions:**

[redacted] b(4)

Medical Officer Comments: *It is agreed that a Warning is warranted for the combined use of telbivudine with pegylated interferon alfa-2a. However, because there have been reports of peripheral neuropathy with telbivudine alone, the Warning should not be limited to the* [redacted] *. The proposed Warning will be modified to include a further description of peripheral neuropathy, information for the provider regarding drug discontinuation when signs and symptoms and neuropathy occur.* b(4)

Additional labeling recommendations will be reviewed for NDA 22-154 upon receipt of the applicant's Complete Response. For NDA 22-011 S-001, additional labeling recommendations will be made after formal submission and review of the REMS and MedGuide as a major amendment to the efficacy supplement.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held to discuss the original NDA, 22-011 for telbivudine, the supplemental NDA 22-011 S-001 or for NDA 22-154.

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/s/

Mary Singer
1/23/2009 11:35:42 AM
MEDICAL OFFICER