7.1.3.3 Other significant adverse events

Due to the antagonist effects of naltrexone at the mu opioid receptor, there is a potential risk for dysphoria and other mood changes, as well as subsequent suicide in naltrexone-treated patients. In a placebo-controlled study in which patients with obesity were randomized to treatment with placebo or oral naltrexone 300 mg/day, 19% of patients in the oral naltrexone group developed non-serious elevations in serum transaminases after 3-8 weeks of treatment, compared to 0% of placebo-treated patients.

The Medisorb Naltrexone database suggested that, as a result of the route of administration, the drug may be associated with injection site reactions. Descriptions of the types of reactions were consistent with an inflammatory type response. The safety database also contained information regarding elevations in eosinophil count, a case of eosinophilic pneumonia, and reports of rash, urticaria, and angioedema. Together, the adverse events were suggestive of an allergic reaction following study treatment.

Therefore the safety database was assessed for evidence of increased risk of suicide, elevated LFTs, and allergic reactions in Medisorb Naltrexone patients. In addition, the specific type and severity of injection site reactions were evaluated.

7.1.3.3.1 HEPATOTOXICITY

Alkermes is of the opinion that the risk of hepatocellular injury from Medisorb Naltrexone is considerably lower than that of oral naltrexone because:

- Whereas the total monthly dose at which hepatotoxicity was observed with oral naltrexone (300 mg/day) would be 8400 mg, the total monthly dose of Medisorb Naltrexone is 380 mg (which is 22-fold lower than the total monthly dose of oral naltrexone).
- Administration of Medisorb Naltrexone suspension by gluteal IM injection avoids first-pass hepatic metabolism.
- Medisorb Naltrexone will be dispensed in single-dose kits and will be administered by a health care provider, reducing the risk of patient overdose.

Upon review of the safety data, Alkermes found that in alcohol-dependent subjects treated with Medisorb Naltrexone suspension the hepatic safety profile was indistinguishable from that of placebo, with assessments of ALT, AST, GGT, and total bilirubin. Also, single-dose IM administration of relatively high doses (141, 269, 530 and 784 mg) of Medisorb Naltrexone to healthy subjects did not result in hepatotoxicity.

Using the datasets *iss-ae_3.xpt* and *iss-labs.xpt* I calculated the number of patients who experienced a liver-related adverse event. I searched *iss-ae_3.xpt* for all terms consistent with hepatocellular injury, first by system organ class (gastrointestinal disorders, hepatobiliary disorders, and investigations), and then by specific terms including: AST, ALT, GGT, ALP,

SGPT, SGOT, LFT, liver, liver function, liver enzyme, laboratory test, aspartate, alanine, bilirubin, alk phos, glutamyltransferase, hepatitis, and jaundice.

I then searched the *iss-labs.xpt* dataset using the variable "LBNAME," under which were coded tests for AST (SGOT), ALT (SGPT), alanine transaminase, aspartate transaminase, total bilirubin, and total bilirubin (mg/dL). These categories were collapsed for ease of analysis. In addition, I used the variable "LBFLAG" to identify all patients with high values for any of the lab tests. This subset of patients was merged with the subset from the *iss-ae.xpt* dataset for comparison of events between active- and placebo-treated patients.

7.1.3.3.1.1 Reviewer's Analysis: Patients with Hepatic-Related Adverse Events

7.1.3.3.1.1.1 Hepatic-related events – Studies of 4-6 month's exposure

Based on the *iss-ae_3.xpt* dataset, 4.8% of all patients (52/1090) in the 4-6 month trials experienced adverse events suggestive of hepatocellular injury. Most patients reported more than one type of hepatic-related injury. Only 1 of these AEs was considered serious (Subject ALK21003-230-024, 190-mg, cholelithiasis) but, based on my review of the patient narrative, was not related to study treatment.

The frequency of hepatic-related AEs in the combined Medisorb Naltrexone subset was 4.6% (37/811). This was lower than the frequency in the placebo group (5.6% (12/124)), and was comparable to the frequency in the oral naltrexone group (4.6% (3/65)). The risk of hepatic-related AEs did not appear to increase with increasing doses of Medisorb Naltrexone: 4.8% (10/210) of the 190-mg patients, 4.5% (26/576) of the 380-mg patients, and 4% (1/25) of the 400-mg patients.

Listed in Table 7.1.3.3.1.1 (below) are the types of events that were hepatic-related.

Liver function test (LFT) abnormalities/increases were the most commonly occurring. Of the 1090 patients with 4-6 months of drug exposure, 67 patients (6.1%) had an elevation of AST, ALT, GGT, bilirubin, or alkaline phosphatase. The most frequent type of LFT abnormality was an elevation in GGT, however more placebo patients than naltrexone patients reported this AE (3.7% of placebo patients vs. 1.6% of Medisorb Naltrexone and 0% of oral naltrexone patients). There was no evidence of a dose response of GGT elevation among the Medisorb Naltrexone groups. The greater proportion of placebo patients with high GGT levels compared to Medisorb Naltrexone patients likely reflects a higher frequency of drinking in the placebo population than in the Medisorb Naltrexone patients.

AST increases were the next most common LFT change, with slightly more patients in the oral naltrexone and combined Medisorb Naltrexone groups (~ 1.5% each) experiencing this AE than in the placebo group (0.9%). With respect to ALT, patients in the combined 380/400-mg Medisorb Naltrexone group and the oral naltrexone groups were more likely to report ALT increases (1.5% and 1.2%, respectively) than placebo patients (0.9%).

Five patients were reported as having hepatitis (1 case of alcoholic hepatitis, and 3 cases of hepatitis C, and 1 case of "hepatitis NOS.")[6]. Two cases occurred during ALK21-003, and the remaining three during ALK21-006. None of the cases was considered serious. I reviewed the patient narratives and CRFs to evaluate for a relationship to study treatment. The narratives showed that patients experienced elevated LFTs either in the context of increased drinking or hepatitis C diagnosis. These factors make it difficult to ascertain whether Medisorb Naltrexone is associated with hepatitis, or whether it increases the risk of hepatitis in patients with predisposing factors.

REVIEWER COMMENT:
Overall, therefore, the data from the trials of 4-6 months' duration suggest that treatment with Medisorb Naltrexone is associated with a slightly increased risk of AST and ALT compared to placebo, however this risk is similar to that associated with oral naltrexone therapy. Therefore, Medisorb Naltrexone does not appear to offer a safety advantage – with respect to hepatotoxicity – over oral naltrexone. The risk of hepatitis following treatment with Medisorb Naltrexone appears to be low.

6 Subject ALK21006-247-006: alcoholic hepatitis; Subject ALK21006-255-004: hepatitis NOS; Subjects ALK21003-216-005, ALK21003-216-012, and ALK21006-252-009: hepatitis C.

Table 7.1.3.3.1.1.1 Reviewer's Analysis: AEs suggestive of hepatocellular injury – 4 – 6 month Studies

SOC	HLT	PT/AE	All subjects N = 1090		Medisorb Naltrexone										Oral NTX N = 65		Placebo N = 214	
					190 mg N = 210		380 mg N = 576		400 mg N = 25		380/400 mg N = 601		All N = 811					
			N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any LFT abnormality			*67*	*6.15*	*12*	*5.72*	*33*	*5.73*	*3*	*12*	*36*	*6.0*	*48*	*5.91*	*4*	*6.16*	*15*	*7*
Investigations	Liver function analyses	GGT increased	21	1.93	4	1.90	8	1.39	1	4.00	9	1.5	13	1.60	0	0.00	8	3.74
		AST increased	15	1.38	3	1.43	8	1.39	1	4.00	9	1.5	12	1.48	1	1.54	2	0.93
		ALT increased	13	1.19	1	0.48	8	1.39	1	4.00	9	1.5	10	1.23	1	1.54	2	0.93
		Liver function tests NOS abnormal	12	1.10	2	0.95	7	1.22	0	0.00	7	1.2	9	1.11	1	1.54	2	0.93
		Hyperbilirubinaemia/ Bilirubin increased	4	0.37	1	0.48	1	0.17	0	0.0	1	0.2	2	0.24	1	1.54	1	0.47
	Tissue enzyme analyses NEC	Alk phos NOS increased	2	0.18	1	0.48	1	0.17	0	0.00	1	0.2	2	0.25	0	0.00	0	0.00
Any hepatitis			*5*	*0.46*	*1*	*0.48*	*4*	*0.69*	*0*	*0.0*	*4*	*0.7*			*0*	*0.0*	*0*	*0.0*
Hepatobiliary disorders	Hepatocellular damage and hepatitis NEC	Hepatitis alcoholic	1	0.09	0	0.00	1	0.17	0	0.00	1	0.2	1	0.12	0	0.00	0	0.00
Infections and infestations	Hepatic viral infections	Hepatitis C	3	0.28	1	0.48	2	0.35	0	0.00	2	0.3	3	0.37	0	0.00	0	0.00
	Liver and spleen infections	Hepatitis NOS	1	0.09	0	0.00	1	0.17	0	0.00	1	0.2	1	0.12	0	0.00	0	0.00

Table 7.1.3.3.1.1.1 Reviewer's Analysis: AEs suggestive of hepatocellular injury – 4 – 6 month Studies (continued)

SOC	HLT	PT/AE	All Subjects N = 1090		Medisorb Naltrexone 190 mg N = 210		380 mg N = 576		400 N = 25		300/400 N = 601		All N = 811		Oral NTX N = 65		Placebo N = 214	
			N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hepatomegaly - total			*3*	*0.27*	*0*	*0.0*	*1*	*0.17*	*1*	*4*	*2*	*0.3*	*2*	*0.25*	*0*	*0.0*	*1*	*0.47*
Hepatobiliary disorders	Hepatobiliary signs and symptoms	Hepatomegaly	2	0.18	0	0.00	1	0.17	1	4.00	2	0.3	2	0.25	0	0.00	0	0.00
Investigations	Physical examination procedures	Liver palpable subcostal	1	0.09	0	0.00	0	0.00	0	0.00	0	0.0	0	0.00	0	0.00	1	0.47
Hepatobiliary disorders	*Cholecystitis and cholelithiasis*	*Cholelithiasis*	*1*	*0.09*	*1*	*0.48*	*0*	*0.00*	*0*	*0.00*	*0*	*0.0*	*1*	*0.12*	*0*	*0.00*	*0*	*0.00*

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