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Study No.: ADF20001
Title: Open label compassionate access programme to provide adefovir dipivoxil to patients with chronic hepatitis B infection.
Rationale: Adefovir dipivoxil was made available to selected chronic hepatitis B infected patients on an open label compassionate basis.
Phase: IV
Study Period: 17 Mar 03 to 9 Oct 05
Study Design: Multi-centre, open label, compassionate access programme Medication was self-administered and all protocol specific evaluations were performed on an outpatient basis. Subjects were seen for a screening visit, baseline visit and then at least every 8 weeks thereafter. If a subject prematurely discontinues from the programme, it was recommended that they be followed for 16 weeks post discontinuation of therapy. Patients continued to receive adefovir dipivoxil until any of the following occurred: Adefovir dipivoxil became commercially available in the country conducting the study. The patient experienced a treatment-limiting adverse event (AE) believed to be related to adefovir dipivoxil. The programme was terminated.
Centres: Taiwan – 10 Sites Korea – 37 Sites Thailand – 2 Sites China – 2 Sites
Indication: Chronic Hepatitis B
Treatment: A daily dose of 10mg adefovir dipivoxil was used in this programme. It was recommended that patients continue to receive lamivudine at a minimum daily dose of 100mg, which is the registered dose for the treatment of adults with chronic hepatitis B.
Objectives: The primary objective of the programme was to provide open label, pre-approval access to adefovir dipivoxil for patients with limited treatment options. The secondary objective was to collect data on the safety of adefovir dipivoxil for regulatory reporting purpose.
Primary Outcome/Efficacy Variable: Not Applicable
Secondary Outcome/Efficacy Variable(s): Safety
Statistical Methods: Not applicable
Study Population: Key Inclusion Criteria EITHER Patients currently receiving lamivudine after at least 6 months of continuous lamivudine therapy for chronic hepatitis B who fulfilled all the following criteria: positive serum HBV DNA $\geq 10^6$ copies/mL at the screening visit AND serum alanine aminotransferase (ALT) levels > 1.3 times the upper limit of the normal range at the screening visit AND signs of decompensated liver disease as evidenced by one or more of the following: serum bilirubin > 2x upper limit of normal prothrombin time > 3 seconds prolonged despite vitamin K administration unless due to prescribed anticoagulant therapy

serum albumin < 3.2g/dl history of ascites, variceal hemorrhage, hepatic encephalopathy Child-Pugh score ≥8 OR Patients who had undergone a liver transplant and had developed virological breakthrough /YMDD variant HBV as evidenced by: positive serum HBV DNA ≥ 10 ⁶ copies/mL at the screening visit AND serum alanine aminotransferase (ALT) levels > 1.3 times the upper limit of the normal range at the screening visit OR Patients with previously documented decompensated liver disease, currently receiving lamivudine with virological breakthrough as evidenced by: positive serum HBV DNA ≥ 10 ⁶ copies/mL at the screening visit AND serum alanine aminotransferase (ALT) levels > 1.3 times the upper limit of the normal range at the screening visit Availability and willingness of subjects to provide written informed consent Exclusion Criteria Pregnancy (or lactation) or, in subjects capable of bearing children, inability/unwillingness to practice adequate contraception Females of child-bearing potential (post-puberty) unwilling or unable to have pregnancy testing at any study visit Subjects participating in, or who qualify for, or have access to, an ongoing study of adefovir dipivoxil.	
Number of Subjects:	
Planned, N	Not Applicable
Entered, N	572
Completed, n (%)	495 (87)
Total Number Subjects Withdrawn, N (%)	77 (13)
Withdrawn due to Adverse Events n (%)	25 (4)
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for other reasons n (%)	52 (9)
Demographics	
N (ITT)	572
Females: Males	124: 448
Mean Age, years (SD)	46.6 (9.8)
Asian, n (%)	572 (100)
Primary Efficacy Results: Not Applicable	
Secondary Outcome Variable(s): See safety results below.	

Safety Results:	
An adverse event (AE) was defined as any AE occurring during adefovir treatment and follow-up periods of the compassionate programme. A serious adverse event (SAE) was defined as any SAE occurring during adefovir treatment and follow-up periods of the compassionate programme.	
Most Frequent Adverse Events – On-Therapy	
Subjects with any AE(s), n(%)	99 (17)
Ascities	10 (2)
Hepatic encephalopathy	9 (2)
Peritonitis bacterial	8 (1)
Hepatic Failure	8 (1)
Oesophageal varices	6 (1)
Serious Adverse Events-On-Therapy	
N (%) [n considered by the investigator to be related to treatment]	55 (10) [6]

Ascites	10 (2) [0]
Hepatic encephalopathy	9 (2) [1]
Peritonitis bacterial	8 (1) [1]
Hepatic failure	8 (1) [0]
Oesophageal varices haemorrhage	6 (1) [0]
Renal failure acute	4 (<1) [0]
Hepatic neoplasm malignant	4 (<1) [0]
Upper gastrointestinal haemorrhage	3 (<1) [1]
Sepsis	3 (<1) [0]
Hepatic cirrhosis	3 (<1) [0]
Jaundice	3 (<1) [0]
Multi-organ failure	3 (<1) [0]
Gastrointestinal haemorrhage	2 (<1) [0]
Gastrointestinal ulcer haemorrhage	2 (<1) [0]
Pancreatitis acute	2 (<1) [1]
Pneumonia	2 (<1) [0]
Urinary tract infection	2 (<1) [0]
Coma hepatic	2 (<1) [0]
Haemorrhage intracranial	2 (<1) [0]
Hepatorenal syndrome	2 (<1) [0]
Blood creatinine increased	2 (<1) [1]
Abdominal discomfort	1 (<1) [0]
Abdominal distension	1 (<1) [0]
Duodenal ulcer	1 (<1) [0]
Oesophageal ulcer	1 (<1) [0]
Peritoneal haemorrhage	1 (<1) [0]
Varices oesophageal	1 (<1) [0]
Bacteraemia	1 (<1) [0]
Beta haemolytic streptococcal infection	1 (<1) [0]
Bronchopneumonia	1 (<1) [0]
Cellulitis	1 (<1) [0]
Disseminated tuberculosis	1 (<1) [0]
Fungaemia	1 (<1) [0]
Gastroenteritis	1 (<1) [0]
Cerebral infarction	1 (<1) [0]
Encephalitis	1 (<1) [0]
Hepatic function abnormal	1 (<1) [0]
Haematuria	1 (<1) [0]
Oliguria	1 (<1) [0]
Renal insufficiency	1 (<1) [1]
Hepatic neoplasm	1 (<1) [0]
Liver carcinoma ruptured	1 (<1) [0]
Metastasis	1 (<1) [0]
Subjects with fatal SAEs, n (%) [related]	20 (3) [1]
Hepatic failure	7 (1) [0]
Hepatic encephalopathy	5 (<1) [1]
Ascities	3 (<1) [0]
Oesophageal varices hemorrhage	3 (<1) [0]
Hepatic cirrhosis	2 (<1) [0]
Hepatic neoplasm malignant	2 (<1) [0]
Blood creatinine increased	1 (<1) [0]
Disseminated tuberculosis	1 (<1) [0]
Hepatic function abnormal	1 (<1) [0]
Hepatorenal syndrome	1 (<1) [0]

Lung infection	1 (<1) [0]
Multiorgan failure	1 (<1) [0]
Peritonitis bacterial	1 (<1) [0]
Renal failure acute	1 (<1) [0]
Sepsis	1 (<1) [0]
Upper gastrointestinal haemorrhage	1 (<1) [1]

Conclusion:

No statistical analysis of efficacy was planned for this compassionate access programme.. Ninety-nine subjects reported non-serious adverse events with the most frequently reported being ascities. Fifty-five serious adverse events were reported. Twenty fatalities were reported, one of which was considered by the investigator to be related to treatment.

Publications:

No Publication

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