17 January 2013
EMA/275269/2013
Committee for Medicinal Products for Human Use (CHMP)

# Hepsera

(Adefovir Dipivoxil)

Procedure No. EMEA/H/C/000485/FUM/062

# Assessment report



**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

# Rapporteur's Assessment Report

# HEPSERA
# (adefovir dipivoxil)

## FUM 62
## (Following renewal)

# Submission of the 5 year data from study GS-00-494 (an NIH study) with ADV+LAM in naïve patients

## EMEA/H/C/485
## Applicant: GILEAD



| | |
|---|---|
| **Rapporteur:** | P. Lechat |
| **Date of this report:** | 20.12.2012 |
| **Date for comments :** | 02.01.2012 |

# 1 INTRODUCTION

In accordance with the letter of undertaking generated at the time of the Hepsera renewal, Gilead is submitting its response to the following Follow-up Measure, which details data generated from study GS-00-494 (a NIH study) for Hepsera:

**Follow-up Measure:**

| Area | Description | Due Date |
|---|---|---|
| Clinical | Submission of 5-year long-term data from Study GS-00-494 (an NIH study) evaluating the safety, antiviral activity and clinical benefit of the combination of ADV 10 mg and LAM 100mg once daily in ADV treatment-naïve patients with chronic hepatitis B. | 31 October 2012 |

# 2 SCIENTIFIC DISCUSSION

At the time of the Hepsera (adefovir dipivoxil) marketing authorisation approval in March 2003, a study was ongoing and being conducted by the National Institutes of Health (NIH) in the USA. Study GS-00-494 examined the benefit of combination therapy with adefovir and lamivudine for the treatment of chronic hepatitis B when compared with adefovir therapy alone. The results of this study formed one of the commitments made by the MAH (Gilead Sciences International Ltd) in the resulting MA Letter of Undertaking.

The final data from study GS-00-494 (a National Institutes of Health, NIH, study) were provided in full as two peer-reviewed references (eCTD seq 25) and were also discussed by the MAH within the response to FUM document and are summarized below.
The first reference of Ghany et al (2012) presents the first 4 years of safety and efficacy data, whilst the second reference Gara et al (2012), presents up to 10 years of long-term follow-up on patients enrolled in GS-00-494.

### 2.1. Randomised Clinical Trial: The Benefit of Combination therapy With Adefovir and Lamivudine for Chronic Hepatitis B (Ghany *et al*, 2012)

Ghany et al drew upon the benefits observed with combination therapy in the treatment of human immunodeficiency virus (HIV), and proposed the same hypothesis to the treatment of chronic hepatitis B. In theory, the benefits of combination therapy are heightened antiviral activity and prevention of drug resistance. Therefore, in the NIH study (GS-00-494) **41 patients were enrolled** with chronic hepatitis B that **may, or may not, have been previously treated with LAM**. **Patients were randomized to receive ADV alone (10 mg/day) or ADV (10 mg/day) + LAM (100 mg/day) for up to 192 weeks.**

Of the 41 patients enrolled, **31 were HBeAg-positive and 31 were naïve** to prior treatment. At **192 weeks, 30 patients remained on ADV alone or ADV+LAM. The results clearly demonstrate that mean reduction in HBV DNA at week 48 was significantly higher in patients taking ADV+LAM compared with ADV monotherapy.** Furthermore, a greater proportion of patients receiving combination therapy had a combined response of additive antiviral response and prevention of antiviral resistance at 1 year (59% versus 26%, p = 0.06) compared with those receiving ADV monotherapy, and **this was significant at 4 years (68%versus 31% respectively, p = 0.03).**

In this study, combination therapy lowered the rate of virological breakthrough and antiviral resistance such that **no patient on ADV+LAM developed genotypic resistance compared to 32% of those on**

**ADV monotherapy.** The advantages of preventing antiviral resistance by using combination therapy was evident at the end of 192 weeks, and consisted of a significantly higher rate of complete viral suppression and HBeAg loss in the combination group compared to the monotherapy group. However, the rate of HBsAg loss was low (1 patient only).
Patients had 3 liver biopsies throughout the course of the study which revealed that there is substantial histological benefit to maintaining undetectable HBV DNA levels for 4 years.
There were significant improvements in fibrosis, including reversal of cirrhosis compared with baseline. Moreover, at week 192 a third of patients had complete resolution of fibrosis and a quarter had a normal liver biopsy. There was no significant difference between treatment paradigms.

### 2.2. Renal Tubular Dysfunction during Long-Term Adefovir or Tenofovir Therapy in Chronic Hepatitis B (Gara et al, 2012)

The majority of patients enrolled in NIH study, GS-00-494, were enrolled into a follow-on safety study to examine patients with chronic hepatitis B on therapy with either ADV or tenofovir (TDF) between 2002 and 2007. Of the 51 patients, 42 were treated with ADV (most on ADV+LAM combination therapy), 4 with TDF or ADV followed by TDF (n=5) for up to 10 years (mean 7.4 years). Patients were examined for evidence of renal tubular dysfunction (RTD) using a new definition which required de novo appearance of at least 3 of 5 features: hypophosphataemia, hypouricaemia, serum creatinine elevation, proteinuria or glucosuria.

Seven patients developed RTD (14%) and time to onset ranged from 22 to 94 months. The estimated 10-year cumulative rate was 15%. Patients with RTD were older (58 versus 44 years; p = 0.01) and had lower baseline glomerular filtration rates compared to those without.
All other features did not differ. Six patients with RTD were switched to entecavir and had improvements in serum phosphate, creatinine, uric acid levels and proteinuria.

### 2.3. MAH's conclusion

The original NIH study (GS-00-494) demonstrated that significant clinical benefit can be achieved by administering a combination of ADV+LAM to patients with chronic hepatitis B. Not only is combination therapy synergistic and additive in terms of efficacy, virological breakthrough and antiviral resistance is minimized when using two distinct nucleoside/nucleotide analogues in combination when compared to monotherapy. This is in accordance with the current Hepsera (adefovir dipivoxil) SmPC.
Furthermore, in-line with data recently reported and included in the Viread (tenofovir disoproxil fumarate) SmPC, long-term suppression of HBV DNA results in significant histological benefits, such as improvements in fibrosis and reversal of cirrhosis.
**This study began prior to the availability of second generation nucleoside analogues, such as TDF and entecavir, which are more potent and have a better resistance profile** (0% at 5 years for TDF, and 1% over 6 years for entecavir; see TDF and entecavir SmPCs) when compared to either ADV or LAM monotherapy (29% and 69%, respectively). However, the study demonstrated value in highlighting alternative treatment paradigms should monotherapy treatment fail.
The second follow-on safety study examined renal tubular dysfunction (RTD) observed as a result of up to 10 years treatment with ADV+LAM, ADV, TDF or TDF following ADV therapy. This safety study was limited by patient numbers and the lack of pre-treatment assessment of urinary phosphate transport and lack of bone and renal biopsies to assess osteomalacia and structural renal damage. However, it was reported that up to 15% of patients (n=7) in the study experienced symptoms of RTD, only one of which was initially on TDF monotherapy. Of the others, 5 were on ADV+LAM and 1 was on ADV followed by TDF. It is recommended within the respective ADV and TDF SmPCs to closely monitor renal function whilst on treatment.

In conclusion, the initial NIH and subsequent follow-on safety study did not reveal any new information on the use of ADV in the treatment of chronic hepatitis B. The MAH proposed at this time not to amend the current SmPC for ADV.

# 3 DISCUSSION AND OVERALL CHMP CONCLUSIONS

*The scope of the present FUM was the submission of the NIH study (also identified as GS-00-494) comparing ADV monotherapy versus de novo LAM+ADV in CHB-infected patients. The study included 41 patients, 31 of which were treatment-naïve patients. The study results show that adefovir should not be used as monotherapy since maintenance of viral suppression was more common with combination ADV+LAM therapy.*
*Of note, the advantage of ADV+LAM combination therapy (as compared to switch to ADV monotherapy) in terms of reducing the risk for resistance in patients with lamivudine-resistance has been fully acknowledged and this strategy was recommended in the Hepsera SmPC in 2008 (through Hepsera Type II33 variation). Whether de novo combination rather than monotherapy would be also of interest in naïve patients might have been a topic for discussion at the time of the study start (2001), notably since at this time the HBV armamentarium was limited to drugs with low to moderate genetic barrier of resistance. However, nowadays, the availability of more potent agents with high genetic barrier for resistance has markedly changed the situation. As stressed by the authors and reflected in the EASL guidelines, with the availability of more potent agents with high genetic barrier for resistance, there is no evidence to favour de novo combination therapy with nucleos(t)ide analogs in naïve patients over monotherapy with entecavir or tenofovir.*

*However, beyond this discussion on mono- versus bi-therapy, the critical issue for Hepsera pertains to its current inappropriate "unqualified" indication in monotherapy.*

*As a reminder, Hepsera was authorised in Europe for the treatment of chronic HBV infected patients in March 2003. The clinical development programme for adefovir dipivoxil enrolled a wide range of patients. More than 1000 patients were included in supportive and pivotal studies that encompassed naives patients with chronic hepatitis B (HBeAg positive and HBeAg negative, respectively) and compensated liver disease, patients with chronic hepatitis B failing lamivudine therapy who have received a liver transplantation or who are waiting for a transplantation, patients with lamivudine-resistant chronic hepatitis B infection, including studies in patients with compensated/decompensated liver disease, and in patients co-infected with HIV.*
*In pivotal studies (in naïve patients) the superiority of adefovir dipivoxil versus placebo was demonstrated regardless of baseline characteristic. The efficacy was consistently observed whatever the type of response: histological, virological biochemical, serological or clinical) the disease subtype (HBeAg positive, negative, compensated or not) and the virus subtype (wild type or YMDD mutants associated with lamivudine resistance). Those data have been reflected in the SmPC at the time of the MA. Of note, the genotypic and phenotypic data derived from the MA clinical studies did not show any mutation induced resistance associated with the use of adefovir dipivoxil but the risk of delayed emergence of resistance was stressed.*

*Since the initial MA, the resistance profile of ADV has proven to be worse than established at the stage of the initial approval. Thus, available long term data have shown a 25% cumulative probability of emergence of resistance at 5 years. Moreover, even though the two key mutations that confer resistance to ADV remain rtN236T and rtA181V, a signal towards a possible impact of the single rt181T mutation on ADV resistance has been more recently identified. As a consequence of the above, change of therapy was recommended in patients with partial virologic response (>1000 copies/ml at or beyond 1 year) and the combined use of ADV and LAM was recommended for the management of LAM-R patients to delay the appearance of ADV resistance and virological breakthrough.*
*As regards the safety, it is worth mentioning that the safety concern for Hepsera mainly pertains to its renal toxicity (risk of renal failure and proximal renal tubulopaty) and adverse events having possible mitochondrial toxicity involvement such as myoptahy, pancreatitis. As for tenofovir, there are remaining uncertainties pertaining to the long term safety data in particular renal events and impact on the bone due to progressive loss of phosphate.*
*The publication from Gara et al. provided in the current submission adds further to this concern since the authors found that "renal tubular dysfunction develops in 15% of patients treated with adefovir*

*(n=42) or tenofovir (n=4) or adefovir followed by tenofovir (n=5) for 2 to 9 years and is partially reversible with change to other antivirals".*

*Moreover, since the MA of Hepsera was granted, the standard of care has evolved. Two medicinal products with both high potency and high genetic barrier to resistance have become the "gold standard" for the treatment of chronic hepatitis B infection in Europe. Those are Baraclude (entecavir) and Viread (tenofovir). Those medicinal products may be considered as major advance for HBV-infected patients and have changed the therapeutic management of patients, at least in Europe. They are recommended as first-line monotherapy in EASL guidelines and have become the medicinal products of choice for initiation of treatment. It is however acknowledged that ADV may still have a role in clinical practice in patients where more recently approved agents are not yet available or affordable and in patients who may be intolerant to TDF or ETV.*

*To this purpose, it appears misleading that the indication for Hepsera puts artificially adefovir at the same level as second-generation nucleoside analogues. Therefore, as previously stated by the CHMP, the SmPC for Hepsera should reflect the fact that* ***ADV can no longer be regarded as an optimal first line monotherapy besides tenofovir or entecavir.***

*Therefore, the indication of Hepsera should be revised to recommend the initiation of Hepsera only as a second line option.*
*This is consistent with the attitude adopted for Zeffix and Sebivo and fully in line with expert recommendation such as those given in the EASL guidelines.*

*For this purpose, it is proposed to* ***revise the SmPC as follows****:*

**"4.1 Therapeutic indications**

Hepsera is indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis. ***Initiation of Hepsera treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.***
- decompensated liver disease ***in combination with a second agent without cross-resistance to Hepsera .***

**4.2 Posology and method of administration**

Therapy should be initiated by a physician experienced in the management of chronic hepatitis B.

*Adults:* The recommended dose of Hepsera is 10 mg (one tablet) once daily taken orally with or without food.
Higher doses must not be administered.

***In patients with decompensated liver disease, adefovir should always be used in combination with a second agent, without cross-resistance to adefovir, to reduce the risk of resistance and to achieve rapid viral suppression."***

*Changes in other sections of the SPC are not deemed necessary.*

***Moreover, with the submission of data from study GS-00-494, the condition in annex II (obligation to conduct post-authorisation measures) has been fulfilled and can therefore be deleted.***