

Table 1. Clinical Model Inputs

Parameter	Value	Source
Annual transition probabilities for disease progression (percentage of patients)		
HBeAg seroconversion to HBeAg negative	2.8%	Hsu 2002 ⁽¹⁾
HBeAg seroconversion to HBeAg positive	3.0%	Shepherd 2006 ⁽²⁾
HBeAg seroconversion to HCC	0.2%	Hsu 2002 ⁽¹⁾
HBeAg seroconversion to HBsAg seroclearance	0.7%	Dakin 2010 ⁽³⁾
HBsAg seroconversion to HCC	0.0%	Dakin 2010 ⁽³⁾
HBV DNA <300 to HBsAg seroclearance	0.2%	Chen 2009 ⁽⁴⁾
CC (on treatment) to DCC	1.4%	Dakin 2010 ⁽³⁾
CC (off treatment) to DCC	5.0%	Fattovich 2003 ⁽⁵⁾
DCC (off treatment) to CC	0.0%	Dakin 2010 ⁽³⁾
DCC (year 1) to CC	13.6%	
DCC (year 2) to CC	0.0%	
DCC to HCC	2.9%	Fattovich 2003 ⁽⁵⁾
DCC to LT	1.6%	Bermingham 2015 ⁽⁶⁾
HCC to LT	1.6%	
MOF risk over 10 years for TDF-based therapies (percentage of patients)		
Low risk (<10%)	5%	University of Sheffield ⁽⁷⁾
Medium risk (≥10% to ≤20%)	15%	
High risk (≥21%)	25%	
MOF vs TDF, hazard ratio		
TAF (vs TDF)	0.956	320-0108 and 320-0110 trials ^(8,9)
ETV (vs TDF)	0.956	Assumed equivalent to TAF vs TDF
Mean change in eGFR from baseline (mL/min)		
TAF		320-0108 and 320-0110 trials ^(8,9)
Year 1	-3.1	
Year 2	-2.5	
Year 3	-2.5	
ETV		Wu 2017 ⁽¹⁰⁾
Year 1	-2.7	
Year 2	-3.7	
Year 3	-4.4	
TDF		Wu 2017 ⁽¹⁰⁾
Year 1	-6.1	
Year 2	-5.0	
Year 3	-4.9	
Excess mortality due to active CHB by HBV DNA levels (IU/mL), hazard ratio		
<300 (undetectable) to 99,999	1.0	Iloeje 2007 ⁽¹¹⁾
100,000–999,999	2.0	
≥1 million	2.1	
Excess mortality due to treatment-related complications, hazard ratio		
Stage 3 CKD	1.36	Neuhaus 2010 ⁽¹²⁾
ESRD	16.80	USRDS 2014 ⁽¹³⁾
MOF	1.26	Bliuc 2013 ⁽¹⁴⁾
Annual mortality risk due to liver-related complications (percentage of patients)		
CC	3.7%	Fattovich 2003 ⁽⁵⁾
DCC	15.6%	
HCC	56.0%	Dakin 2010 ⁽³⁾
LT (first year)	21.0%	Veenstra 2007 ⁽¹⁵⁾
Post-LT (subsequent years)	5.75%	

Abbreviations: CC, compensated cirrhosis; CHB, chronic hepatitis B; CKD, chronic kidney disease; DCC, decompensated cirrhosis; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LT, liver transplant; MOF, major osteoporotic fracture; TAF, tenofovir alafenamide fumarate; TDF, tenofovir diphosphate fumarate.

Table 2. Health Utilities

Health state		Health utility	Source
Liver disease health states			
No cirrhosis–viremic		0.68	Levy 2008 ⁽¹⁶⁾
No cirrhosis–viral suppression		0.77	
Compensated cirrhosis–viremic		0.68	
Compensated cirrhosis–viral suppression		0.69	
Decompensated cirrhosis		0.35	
Hepatocellular carcinoma		0.38	
Liver transplant		0.57	
Post-liver transplant		0.67	
Flare		0.03	Assumption
HBeAg seroconversion, by years of age	18–29	0.97	Assumption of 1% lower than HBsAg seroclearance
	30–39	0.96	
	40–49	0.95	
	50–59	0.91	
	60–69	0.81	
	70–79	0.79	
	≥80	0.73	
HBsAg seroclearance, by years of age	18–29	0.98	Levy 2008 ⁽¹⁶⁾
	30–39	0.97	
	40–49	0.96	
	50–59	0.92	
	60–69	0.82	
	70–79	0.79	
	≥80	0.74	
Major osteoporotic fracture states			
Average utility multiplier, year 1		0.729	Calculated based on Talevski 2021 ⁽¹⁷⁾
Average utility multiplier, year 2+		0.729	
Renal disease states			
Annual stage 3 CKD		0.80	Calculated based on Cooper 2020 ⁽¹⁸⁾
Average ESRD utility multiplier		0.76	

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

Table 3. Cost inputs

Parameter	Cost	Source
Annual treatment acquisition costs		
TAF	€2,936	Hellenic Association of Pharmaceutical Companies 2021 ⁽¹⁹⁾
TDF (88% generic)	€1,431	
ETV (74% generic)	€2,990	
TAF+ETV	€5,926	
TDV+ETV	€4,421	
Annual liver-related costs		
No cirrhosis	€635	Athanasakis 2015 ⁽²⁰⁾ & Athanasakis 2013 ⁽²¹⁾
Compensated cirrhosis	€1,330	Gountas 2017 ⁽²²⁾
Decompensated cirrhosis	€4,426	
Hepatocellular carcinoma	€21,621	Athanasakis 2015 ⁽²⁰⁾ & Athanasakis 2013 ⁽²¹⁾
Liver transplant	€34,620	Veenstra 2007 ⁽¹⁵⁾
Post-liver transplant	€3,952	
HBeAg seroconversion	€635	Assumed same as no cirrhosis
HBsAg seroconversion	0	Assumed to be 0
Major osteoporotic fracture costs per event		
Hip	€12,111	Hernlund 2013 ⁽²³⁾
Vertebral	€2,679	
Forearm/wrist	€740	
Weighted average cost*	€5,268	
Annual renal disease costs		
Stage 3 CKD	€866	Cicchetti 2011 ⁽²⁴⁾
Dialysis	€33,594	Kaitelidou 2005, ⁽²⁵⁾ Kontodimopoulos 2007, ⁽²⁶⁾ Naoum 2016 ⁽²⁷⁾
Transplant	€33,617	
Weighted average cost of ESRD, year 1	€33,600	Calculation [†]
Weighted average cost of ESRD, year 2	€24,859	
CHB-related costs per event		
Resistance	€635	Assumed same as no cirrhosis
Flare	€369	Assumed equal to 1-month cost of decompensated cirrhosis
Treatment switch	€59	Assumed 16% of flare
Death	€6,952	Ovaguez 2017 ⁽²⁸⁾

*Weighted average cost that 34.5% of fractures will be hip, 31.3% will be vertebral, and the remaining 34.2% will be forearm/wrist.⁽²⁹⁾

†Weighted average cost that 74.0% of ESRD patients are on dialysis and 26.0% receive a transplant.

Abbreviations: CHB, chronic hepatitis B; CKD, chronic kidney disease; ESRD, end-stage renal disease; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

References

1. Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology*. 2002;35:1522-7.
2. Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. *Health Technol Assess*. 2006;10.
3. Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naïve patients with chronic hepatitis B. *Value Health*. 2010;13:934-45.
4. Chen CJ, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology*. 2009;49:S72-84.
5. Fattovich G. Natural history of hepatitis B. *J Hepatol*. 2003;39 Suppl 1:S50-8.
6. Bermingham SL, Hughes R, Fenu E, Sawyer LM, Boxall E, Kennedy PT, Dusheiko G, et al. Cost-effectiveness analysis of alternative antiviral strategies for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in the United Kingdom. *Value Health*. 2015;18:800-9.
7. Foundation for Osteoporosis Research and Education. 10-year fracture risk calculator version 2.0. 2015.
8. Chan HL, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, Hui AJ, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1:185-95.
9. Buti M, Gane E, Seto WK, Chan HL, Chuang WL, Stepanova T, Hui AJ, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1:196-206.
10. Wu IT, Hu TH, Hung CH, Lu SN, Wang JH, Lee CM, Chen CH. Comparison of the efficacy and safety of entecavir and tenofovir in nucleos(t)ide analogue-naïve chronic hepatitis B patients with high viraemia: a retrospective cohort study. *Clin Microbiol Infect*. 2017;23:464-9.
11. Iloeje UH, Yang HI, Jen CL, Su J, Wang LY, You SL, Chen CJ. Risk and predictors of mortality associated with chronic hepatitis B infection. *Clin Gastroenterol Hepatol*. 2007;5:921-31.
12. Neuhaus J, Angus B, Kowalska JD, La Rosa A, Sampson J, Wentworth D, Mocroft A. Risk of all-cause mortality associated with nonfatal AIDS and serious non-AIDS events among adults infected with HIV. *Aids*. 2010;24:697-706.
13. United States Renal Data System (USRDS). 2014 Annual Data Report. Volume 1: CKD. Chapter 3: Morbidity and Mortality. 2014.
14. Bliuc D, Nguyen ND, Nguyen TV, Eisman JA, Center JR. Compound risk of high mortality following osteoporotic fracture and refracture in elderly women and men. *J Bone Miner Res*. 2013;28:2317-24.
15. Veenstra DL, Sullivan SD, Clarke L, Iloeje UH, Tafesse E, Di Bisceglie A, Kowdley KV, et al. Cost effectiveness of entecavir versus lamivudine with adefovir salvage in HBeAg-positive chronic hepatitis B. *Pharmacoeconomics*. 2007;25:963-77.
16. Levy AR, Kowdley KV, Iloeje U, Tafesse E, Mukherjee J, Gish R, Bzowej N, et al. The impact of chronic hepatitis B on quality of life: a multinational study of utilities from infected and uninfected persons. *Value Health*. 2008;11:527-538.
17. Talevski J, Sanders KM, Busija L, Beauchamp A, Duque G, Borgström F, Kanis JA, et al. Health service use and quality of life recovery 12 months following major osteoporotic fracture: latent class analyses of the international costs and utilities related to osteoporotic fractures study (ICUROS). *J Bone Miner Res*. 2021;36:252-61.
18. Cooper JT, Lloyd A, Sanchez JJG, Sörstadius E, Briggs A, McFarlane P. Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. *Health Qual Life Outcomes*. 2020;18:310.
19. Hellenic Association of Pharmaceutical Companies. Price Bulletin. 2021.
20. Athanasakis K, Ferrante SA, Kyriopoulos II, Petrakis I, Hill M, Retsa MP, Kyriopoulos J. Boceprevir for chronic Genotype 1 hepatitis C virus in the current health care setting in Greece: a cost-effectiveness analysis. *Clin Ther*. 2015;37:1529-40.
21. Athanasakis K, Arzoumanidou D, Petrakis I, Karampli E, Theodoropoulou T, Retsa MP, Kyriopoulos J. A cost-of-illness analysis of hepatitis C in Greece. *Value Health*. 2013;16:A496.
22. Gountas I, Sypsa V, Anagnostou O, Martin N, Vickerman P, Kafetzopoulos E, Hatzakis A. Treatment and primary prevention in people who inject drugs for chronic hepatitis C infection: is elimination possible in a high-prevalence setting? *Addiction*. 2017;112:1290-9.
23. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*. 2013;8:136.
24. Cicchetti A, Ruggeri M, Codella P, Ridolfi A. The health and social costs of chronic kidney disease in Italy. *Farmeconomia Health Econ Ther Pathways*. 2011;12:21.
25. Kaitelidou D, Ziroyanis PN, Maniadakis N, Liapopoulos LL. Economic evaluation of hemodialysis: implications for technology assessment in Greece. *Int J Technol Assess Health Care*. 2005;21:40-6.

26. Kontodimopoulos N, Niakas D. An estimate of lifelong costs and QALYs in renal replacement therapy based on patients' life expectancy. *Health Policy*. 2008;86:85-96.
27. Naoum P, Topkaroglou I, Kitsonis D, Skroumpelos A, Athanasakis K, Iatrou C, Boletis J, et al. Cost calculations during "dire straits": a cost-of-illness analysis of regular hemodialysis for end-stage renal disease in Greece. *Int J Artif Organs*. 2016;39:87-9.
28. Oyagüez I, Buti M, Brosa M, Rueda M, Casado MA. Cost-effectiveness and clinical impact of antiviral strategies of HBeAg-positive and -negative chronic hepatitis B. *Ann Hepatol*. 2017;16:358-65.
29. Svedbom A, Hernlund E, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, et al. Osteoporosis in the European Union: a compendium of country-specific reports. *Arch Osteoporos*. 2013;8:137.