Aestimo
Innovator's Briefing
Hepatitis B

www.aestimo.ie

About the disease

Epidemiology

Global incidence
1 to 1.5 per 100000 people
(route of transmission dependent)

Prevalence in this geography
1 561 000
(chronic cases)

Phases of Chronic Hepatitis B infection		
Phase	**Viral indicators**	**Pathology indicators**
1*	Serum HBVe antigen positive/ high viral load/ HBVe antibody negative	Little to none liver inflammation/normal liver function/clonal hepatocyte expansion/highly contagious
2	Serum HBVe antigen positive/ high viral load/ HBVe antibody negative	Clear indication of altered liver function/ mild inflammation
3	Serum HBVe antigen negative/ Serum HBVs antigen low/ Undetectable to low viral load/ HBVe antibody positive	Little to none liver inflammation/ normal liver function
4	Serum HBVe antigen negative/ moderate viral load/ HBVe antibody positive	Clear indication of altered liver function/ Fibrosis and inflammation present/ patients have many HBV variants
5	Serum HBVs antigen negative/HBVc antibody positive/undetectable viral load in serum but is found in liver	Normal liver function/if patients have developed cirrhosis before loss of HBVs antigen they are at high risk of developing liver cancer

**Phase 1: more prevalent in perinatal based (vertical) viral transmission*

Key characteristics

- 2 billion people worldwide are infected with hepatitis B virus (HBV); 350–500 million have chronic infections, resulting to between 0.8 and 1.2 million deaths worldwide, annually.
- The chronic phase of the disease is associated with immune impairment function to eliminate the virus.
- Infection occurs in hepatocytes, with stable integration of the HBV DNA into the cellular DNA
- The integration event introduces deletions and translocations, while, uniquely for DNA viruses, uses reverse transcriptase during its lifecycle, that has no proof-reading capability resulting in further mutations (rate of 2×10^4 base substitutions/site/year). These mutations occur in all 4 ORFs of the virus.
- Patients with chronic hepatitis B can develop end-stage liver diseases: cirrhosis, liver failure, and liver cancer, while HBV infection is one of the most common reasons for liver transplantation worldwide.
- Prevalence varies significantly as a function of geography, that has also been linked to genotype and subgenotype (each have their own geographic prevalence).
- 10 genotypes (A through J) have been identified with further sub genotypes in groups A to D: these have geographic prevalence, mutation rates and therapy resistance.
- Mass vaccination has generated improvements in viral control: albeit vaccination escape mutations do occur at low frequency, mainly linked to the mutant strains with changes in the surface proteins (results in lower diagnostic sensitivity and treatment response)

- Transmission prevalence is also defined by endemic levels of modes of transmission: in countries endemic for the virus, vertical (mother to infant or perinatal) transmission is a major route, in countries with opioid user issues, shared needles represents a major route of transmission.
- Antiviral treatment has been developed that blocks the viral Lifecyle, but does not eliminate it: efficacy of the intervention types varies within the same classes. Some interventions have been reported to result in higher frequency generation of treatment escape mutants.
- Similar to many infectious diseases treatment continuation or cessation can represent a catch-22: ideally you do not want patients to be permanently treated and guidelines indicate that treatment should stop when serum viral DNA is undetectable, seroconversion has occurred and liver function markers have returned to normal
- However treatment cessation can result in high rates of relapse, while continued treatment results in generation of escape mutants that may influence the pathogenesis and enable the emergence of future potent variants

The Patient Journey

Patient visits primary care physician/family doctor with following symptoms*:

- Fatigue
- Fever and/or general malaise
- Nausea and vomiting
- Dark urine
- Clay coloured faeces
- Possible jaundice
- Abdominal pain

**not all newly infected patients manifest symptoms*

Patient referred to specialist centre:

- Medical history check
- Physical examination
- Liver function tests
- Hepatitis B virus tests (and other virus tests: HIV, Hep C, Hep D)
- Abdominal ultrasound (elastography)

**NB: first degree relatives and sexual partners also need to be tested (and if negative for viral tests, are vaccinated)*

confirmation

Patient referred for treatment:

- Nucleoside Analogues
- Nucleoside reverse transcriptase inhibitor
- Interferon

Follow up patient care and management

- Year 1: Every 3 months; viral testing and liver function tests
- Year 2 onwards: same tests but every 6-12 months

Disease continuation/Recurrence:

- Lifelong treatment often needed
- Drug resistance mutations occur because of sustained treatment
- >50% of patients will relapse within 10 years if they stop therapy (treatment stopped because serum virus tests have indicated viral clearance)
- Vaccine escape mutants occur around 0.1% of the time

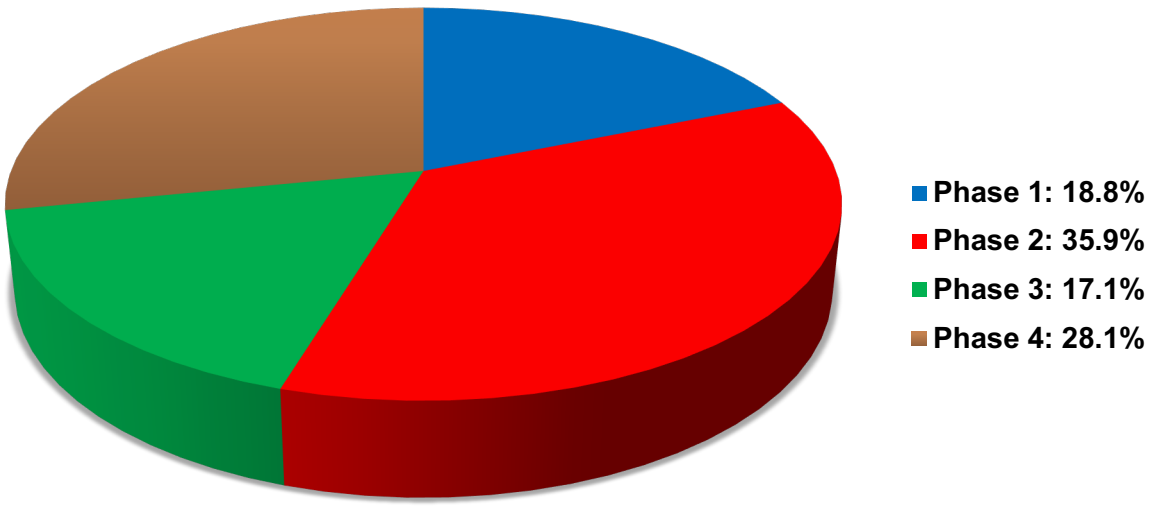
Standards-of-Care, Prices and Market size

- **Treatment Cost (TC)** represents the precise treatment regimen (annual or recommended duration if < 1year) multiplied by the price of the intervention(s) sourced from published prices from the marketplace geography and are indicated in $US equivalent values.
- The **market size** of the intervention, the **Serviceable Available Market (SAM)** value, are annual values and calculated as a function of the patient population eligible for that particular treatment multiplied by the TC.

Treatment description	Example (s)	TC ($US)	SAM ($US Mn)
nucleoside analogue	entecavir	5300	8273.3
nucleoside reverse transcriptase inhibitor	tenofovir	5256	8204.6
interferon	pegasys	21000	32781.0

Global Innovation Development

Number of clinical trials ongoing: 181 globally



Clinical trial characteristics

Phase 1

CT cost $ 895 000

Median Patient No. 90
Median Duration: 3 (months)

Phase 2

CT cost $ 5 400 000

Median Patient No. 100
Median Duration: 9 (months)

Phase 3

CT cost $ 20 328 000

Median Patient No. 242
Median Duration: 12 (months)

Marketplace Forecasting and Development Risk

To estimate risk for innovation development, **forecasted SOM values** are calculated assuming the final product has a **14 year marketplace lifespan with a 21% SAM penetration**, which are then used in indication specific rNPV calculations; following the Health Economics caveat that **the innovative solution will be better than that standard of care (comparator product) but sold at the same price**

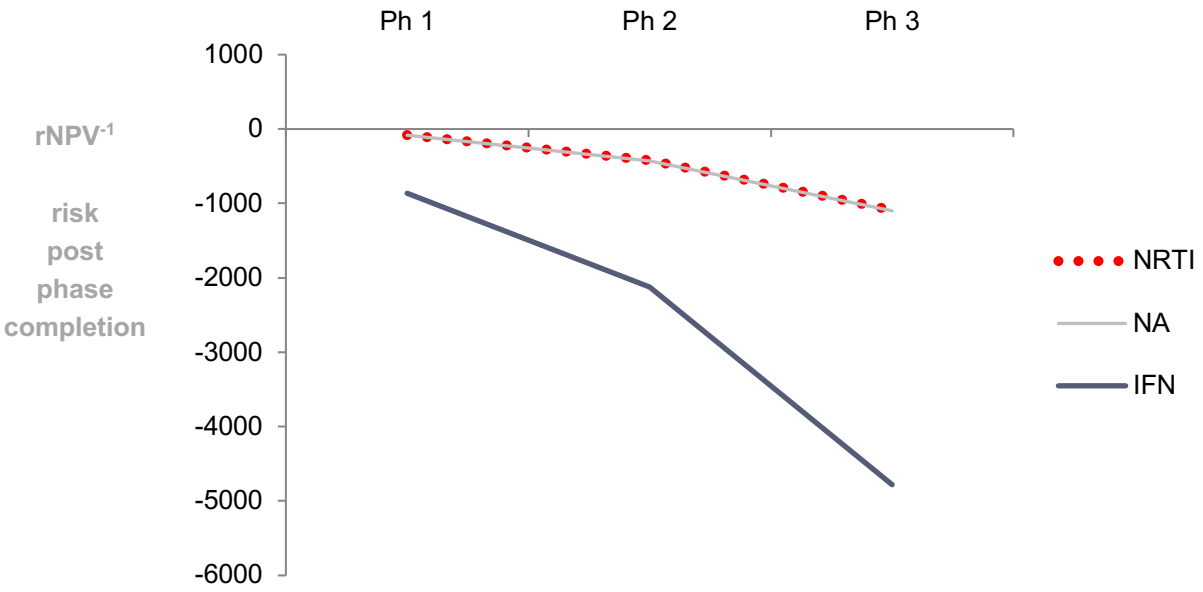
Class	SOM ($US Mn)
nucleoside analogue	24406.2
nucleoside reverse transcriptase inhibitor	24203.6
interferon	96704.0

To reach a balance of zero following innovation investment, integrating in indication specific parameters, required lifetime SOMs are:

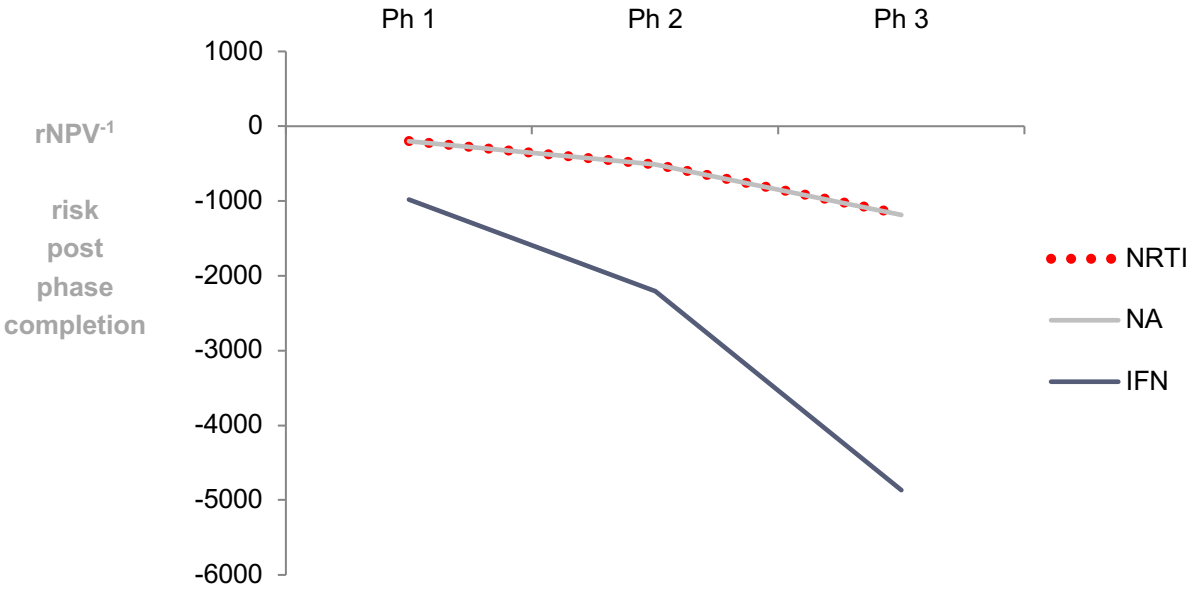
- **1870 $Mn for Repositioning**
- **3330 $Mn for De Novo**

Modeling the creation of a new solution, in which reimbursement agencies will use the standard-of-care as the comparator (clinical benefit and cost benefit), aiming towards generating a higher patient benefit but with the same overall cost, we can estimate the development risk of that new solution. Risk is presented as $rNPV^{-1}$ in which the lower the value the lower the risk. Any risk value above 0, arguably carries too high a development risk with consequent ROI's of <1. More details on the model parameters are explained below.

De Novo development risk:



Repositioning development risk:



Development Risk: model parameters

Development risk assessment was calculated using rNPV methods with the following most optimistic conditions:

De Novo and Repositioning risk measurement conditions

i) Product characteristics

- The new innovation will be superior to the existing standard of care, but will be priced equivalently (best case scenario)
- That the innovative product is a disruptive new 'best-in-class', compared to the standard of care
- That over its lifetime, the product, will achieve an overall 21% Serviceable Obtainable Market, equally over the studied geographic space, and that all citizens have equal access to the product
- The percent of the target population eligible for the intervention, based upon existing treatment regimens within the 'indication and intervention class' are used to create the market uptake

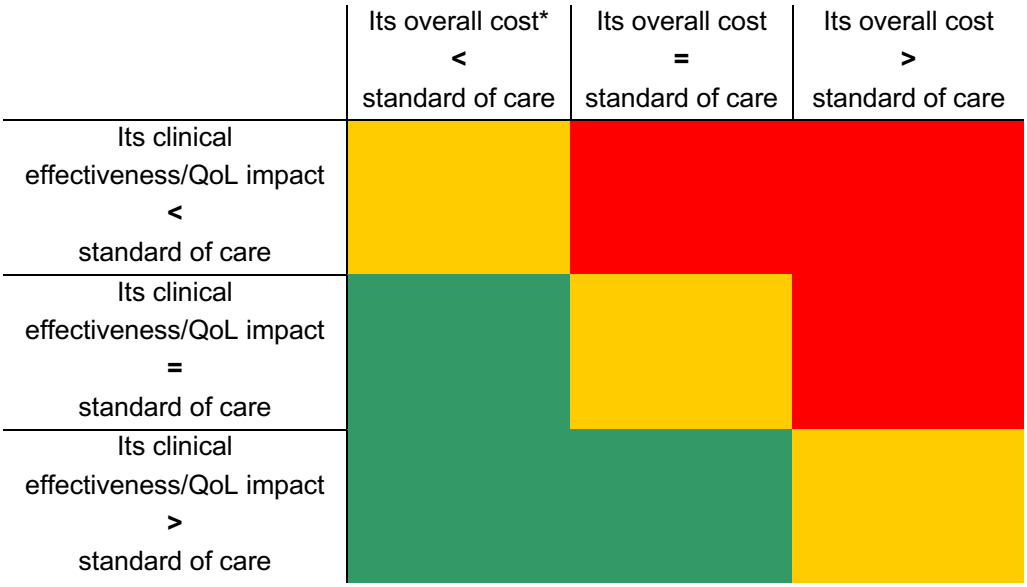
**detailed information on standards of care can be found at drugbank. go.drugbank.com (description, application, structure, DDI, development, manufacturer)*

ii) Valuation characteristics

- Disease Indication and phase specific clinical success rates are used
- Cost of capital risk rates are used
- Disease specific clinical trial metrics are used
- HEOR (Health Economics and Outcome Research) clinical evidence multiple requirements is used
- SOMs are based upon local pricing structures (in this case imported from India)
- For '***De Novo***' Full value chain costs, from experimental development up to first scaled up manufacturing prior to market release are used
- For '***Repositioning***' Full value chain costs, from the end of phase 1, up to first scaled up manufacturing prior to market release are used
- Risk is presented as $rNPV^{-1}$

(During development, risk going down does not necessarily mean value going up due to long term aggregate market influencers)

Health Economics and Outcomes: how will your solution compare to the Standard-of-Care?



- If your solution has the characteristics of the cross-references in **red**, it is highly unlikely any agency or insurance company will agree to the purchase of your product
- If your solution has the characteristics of the cross-references in **amber**, the agencies or insurance companies will perform an Incremental Cost Effectiveness Review (ICER) to determine if it is worth purchasing your product
- If your solution has the characteristics of the cross-references in **green**, it is highly likely that all agencies and insurance company will agree to the purchase of your product

**Cost: this does not mean the price of the intervention exclusively. This includes evidence indicated below, that also includes operational costs for healthcare facilities, capital expenditures, staff training, procedure changes and monitoring, long term impact on quality of life and associated healthcare costs.*

To arrive at a point of reimbursement, and a customer paying for it, agencies attach a significant amount of emphasis to patient reported outcomes (PROs) that reflects an impact on the Quality of Life (QoL); these are not clinical efficacy endpoints. These are based upon questionnaires presented to the patient during the trial and when approved during treatment, that scales the impact of the intervention as a function of what the patient tells the doctor.

Common key HEOR evidence requirements

The predominant process for HEOR value-for-money assessments by authorities and payers are so called 'health technology assessments'. Each European Union country and sometimes its subregions use HEOR and HTA with varying preferences to certain components of the evidence file. We would recommend that the reader also read the EUnetHTA Core Model as an introduction to understanding these requirements. Typical information requirements are indicated below.

- Details of clinical trials and (if available) real world evidence for new product
- Clinical & economic systematic literature reviews (for new product and comparators and other required evidence)
- Comparative effectiveness vs. standard of care in clinical practice (often more than one comparator will be required)
- Pricing
- Budget impact analyses (financial consequences/change in expenditure of adopting a new intervention)
- Cost-effectiveness analyses (of the new product vs. its comparators that is country dependent), i.e. cost-utility analyses (e.g. Euro or £ per quality adjusted life year (QALY)). In these countries the cost-effectiveness is then measured vs. an established cost-effectiveness threshold. However, cost-effectiveness is not the only decision criterion in these countries.

Other countries (typically those with more decentralised healthcare systems), e.g. Germany, France, Switzerland, Italy, Spain, etc., assess the added benefit of the new technology vs. its comparators followed by a pricing negotiation or reference pricing

Characteristics of HEOR requirements for Hepatitis B *

The HRQoL questionnaires used for assessing quality of life in sufferers of Hepatitis B are:

HBQOL	Hepatitis B quality of life instrument
LDQOL	Liver Disease Quality of Life Questionnaire
CLDQ	Chronic Liver Disease Questionnaire
CHBQOL	Chronic Hepatitis B quality of life instrument
SF-36	RAND Medical Outcomes Study Short Form 36
EuroQOL EQ-5D	EuroQOL Group non-disease specific QoL instrument
WHOQOL-BREF	World Health Organization Quality of Life abbreviated version

**in addition to disease questionnaires, additional QoL questionnaires on fatigue (FIS) depression and anxiety are also used.*

Innovators need to carefully consider the patient outcome benefit from multiple perspectives to ensure their innovation is addressing all stakeholder needs.

We would recommend reviewing the outcomes that can be reported from the QoL questionnaires and address how to integrate them into the innovation development plan to address later stage needs, and increase the value of their solution.

Recommended reading

Subject matter	Type	Author	Link
Hepatitis B epidemiology	website	WHO	https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
Hepatitis B epidemiology	Website/article	Scientific and medical specialists/ The Lancet	https://www.thelancet.com/clinical/diseases/hepatitis-b
Hepatitis B pathogenesis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5989240/
Hepatitis B pathogenesis	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/books/NBK555945/
Follow up of Hepatitis B	website	CDC	https://www.cdc.gov/hepatitis/hbv/HBV-RoutineTesting-Followup.htm
Clinical practice guidelines for Hepatitis B	Peer reviewed publication	Scientific and medical specialists/EASL	https://easl.eu/wp-content/uploads/2018/10/HepB-English-report.pdf
Overview of hepatitis B virus mutations and their implications in the management of infection	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4698481/
About Hepatitis B	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4381181/
Hepatitis B resistance mutations	Peer reviewed publication	Scientific and medical specialists	https://www.nature.com/articles/s41598-019-44604-6
HEOR for Hepatitis B	Peer reviewed publication	Scientific and medical specialists	https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.21692
HEOR for Hepatitis B	Peer reviewed publication	Scientific and medical specialists	https://www.jhep-reports.eu/article/S2589-5559(20)30033-1/pdf
HTA systems in Europe	website	EUPATI	https://toolbox.eupati.eu/resources/hta-systems-in-europe/
EU HTA core model	guidelines	EUnetHTA	https://www.eunethta.eu/hta-core-model/
Evolving HTA approaches in EU countries	Peer reviewed publication	Scientific and medical specialists	https://link.springer.com/article/10.1007/s10198-019-01037-2
Medtech position paper on HTA for IVD	report	Medtech europe	https://www.medtecheurope.org/wp-content/uploads/2017/07/HTA-for-IVDs-in-the-Context-of-Market-Access-update-June-2017_0.pdf
Medtech position paper on HTA for Medtech	report	Medtech europe	https://www.medtecheurope.org/wp-content/uploads/2017/07/Medical-Device-industry-position-on-HTA-update-June-2017.pdf

Your next step

If you are motivated to design new solutions and products that will provide a better Standard of Care, Aestimo is able to provide tailored strategic insights, support and/or advice.

These solutions can provide **higher granularity information** on:

- Reimbursed interventions and solutions (all products in all classes: SOM, forecasted SAM and development risk)
- Solutions in development
- Disease subtypes; prevalence, evidence requirements, clinical trial design, measurements and outcomes
- Repositioning strategies: international growth, additional indications, new indications
- Country specific regulation and evidence requirements
- Feasibility assessments: stakeholders, opportunities, partners, non dilutive funding, product launches

And support the company to develop the evidence and engage with reimbursement authorities and payers.

To talk to us about your needs and plans, please contact Jonathan at jdando@aestimo.ie to schedule a webconference.

Aestimo Innovator's Briefings (AIB)

Bring together

- Marketplace specific standards of care (health products) for each class of intervention used within the indication
- Standard of care specific treatment regimens (dose and duration)
- Marketplace specific prices of standards of care
- Indication specific prevalence and incidence
- Eligible patient populations for each intervention and treatment
- Clinical trial logistic requirements
- Indication specific clinical trial success rates, durations and patient numbers
- Modeled optimal and realistic valuations based upon Serviceable Obtainable Market within a market place for each intervention class
- HEOR evidence requirements
- Development risk and opportunity calculations for *de novo* generation or repositioning of innovations, using full value chain economic costing.

These briefings link together all the key components of the value chain (concept to genericisation) in healthcare intervention development to enable any innovator to assess opportunity and risk for their idea, intellectual property, investment or intervention pipeline.

They also provide logistic and strategic insights that enable the innovator to design global innovation development and launch plans, by understanding what commercialisation action should be taken, when it should be done and where it should be made.