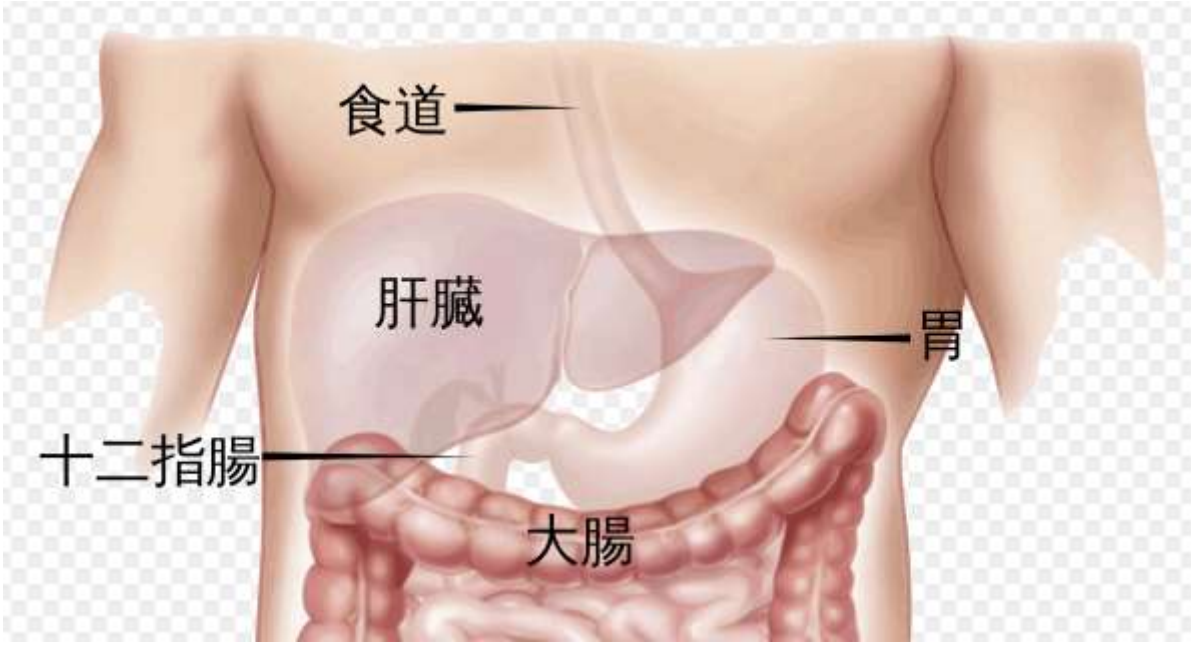
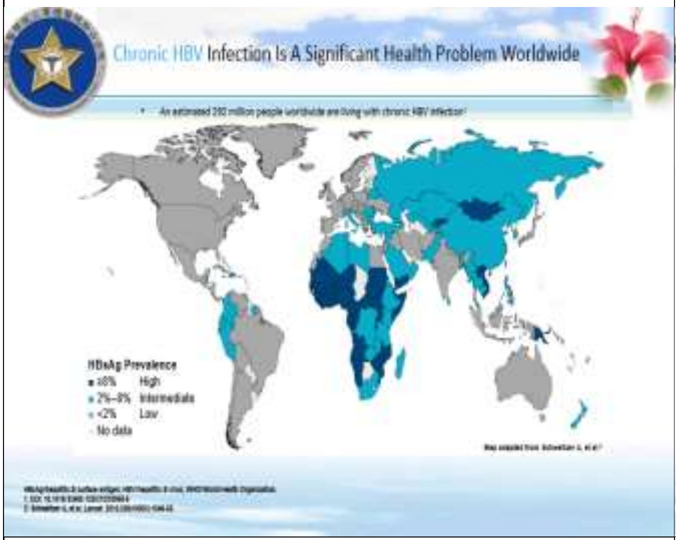
肝炎防治

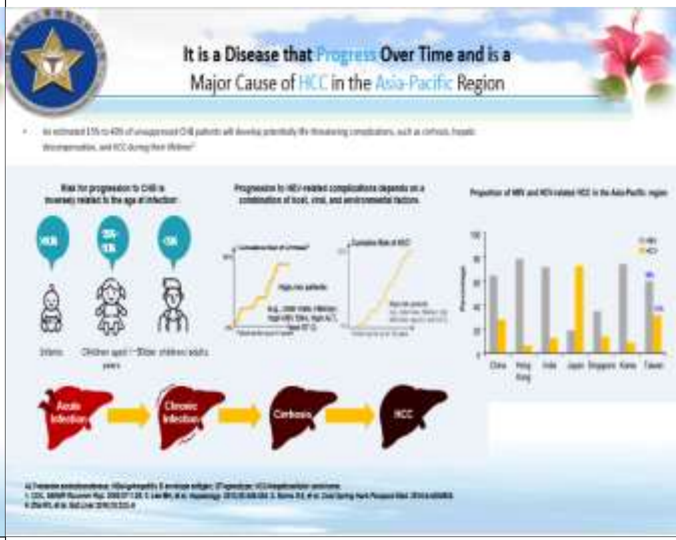


三軍總醫院松山分院教學副院長-周華康主治醫師

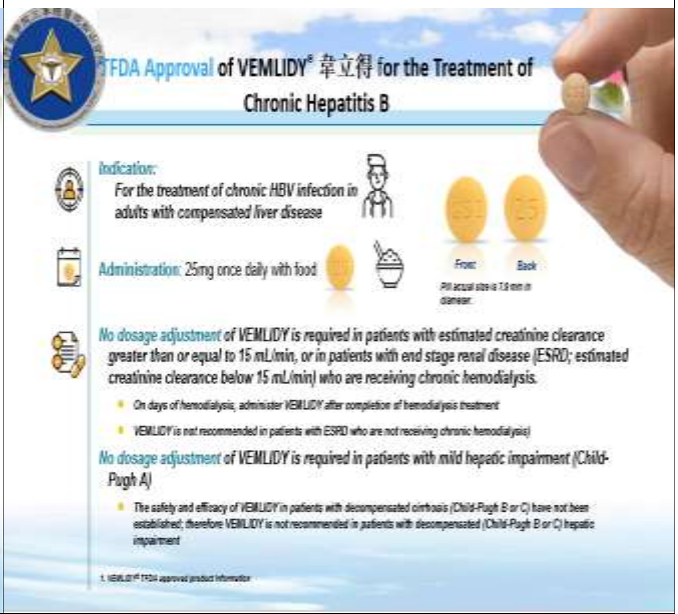
QR code 掃描可得到講義資料

B 型肝炎防治


Chronic HBV Infection Is A Significant Health Problem Worldwide
HBsAg Prevalence
≥8% High
2%–8% Intermediate
<2% Low
No data


It is a Disease that Progress Over Time and is a
Major Cause of HCC in the Asia-Pacific Region
Acute infection
Chronic infection
Cirrhosis
HCC


This Can Be Achieved with A Simple Antiviral Treatment Reaching
Short-Term to Long-Term Goals
1. Host factors:
Older age, male gender, cirrhosis stage, genetic predisposition
2. Viral factors:
HBeAg, elevated HBV DNA, elevated serum ALT level, HBV genotype and mutant type
3. Environmental factors:
Alcohol drinking, cigarette smoking, aflatoxin exposure and probably air pollution
Short-Term
Mid-Term
Long-Term


TFDA Approval of VEMLIDY® 韋立得 for the Treatment of
Chronic Hepatitis B
Indication:
For the treatment of chronic HBV infection in adults with compensated liver disease
Administration: 25mg once daily with food
Front
Back
No dosage adjustment of VEMLIDY is required in patients with estimated creatinine clearance greater than or equal to 15 mL/min, or in patients with end stage renal disease (ESRD; estimated creatinine clearance below 15 mL/min) who are receiving chronic hemodialysis.
On days of hemodialysis, administer VEMLIDY after completion of hemodialysis treatment
VEMLIDY is not recommended in patients with ESRD who are not receiving chronic hemodialysis
No dosage adjustment of VEMLIDY is required in patients with mild hepatic impairment (Child-Pugh A)
The safety and efficacy of VEMLIDY in patients with decompensated cirrhosis (Child-Pugh B or C) have not been established; therefore VEMLIDY is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment


Vemlidy (韋立得) is reimbursed in Taiwan and is the
recommended first-line treatment by all international guidelines


Study 108 & 110
Global Phase 3 CHB Studies: 191 Sites, 19 Countries
873 HBeAg+, 425 HBeAg- CHB Patients*
Study design
Two phase III, randomized, double-blind, active-controlled trials
Key inclusion criteria (both studies)
HBV DNA ≥20,000 IU/mL
ALT >60 U/L (males), >38 U/L (females)
eGFR ≥50 mL/min
GT B/C
Taiwan 8 Sites
S. Korea 21 Sites
Japan 20 Sites
Singapore 3 Sites
China 30 Sites
Hong Kong 5 Sites
Double-blind
Study is ongoing
Baseline
Week 48
Week 96
Week 144
Week 384

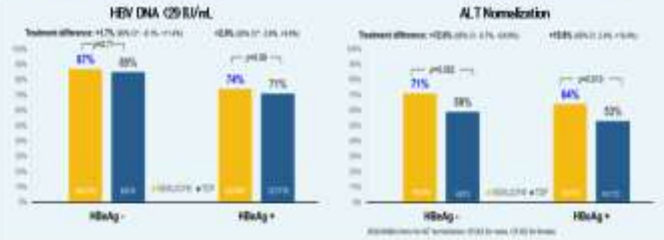
Baseline Demographics & Characteristics

[illegible] of the patients were treatment experienced in the studies–reflecting patients you would see in daily clinical practice

Characteristic	VEMLIDY® (n = [illegible])	TDF (n = [illegible])
Mean age, y (range)	[illegible]	[illegible]
Male, n (%)	[illegible]	[illegible]
Asian, n (%)	[illegible]	[illegible]
Mean body mass index, kg/m² (SD)	[illegible]	[illegible]
Nucleos(t)ide experienced, n (%)	[illegible]	[illegible]
HBV genotype, n(%)		
A	[illegible]	[illegible]
B	[illegible]	[illegible]
C	[illegible]	[illegible]
D	[illegible]	[illegible]
HBeAg positive, n (%)	[illegible]	[illegible]
Mean HBV DNA, log_{10} IU/mL (SD)	[illegible]	[illegible]
Median ALT, U/L (IQR)	[illegible]	[illegible]
FibroTest score ≥ 0.75, n/n (%)	[illegible]	[illegible]

Study 108 & 110

Efficacy: Viral Suppression and ALT Normalization in Patients Receiving TAF or TDF at Week 144



Study 108 & 110

Safety at Week 144

Patients, n (%)[1]	VEMLIDY® (n = 866)		TDF (n = 252)	
Adverse events				
Any AE	702	(81)	198	(79)
Grade 3-4 AE	68	(8)	19	(8)
Serious AE	83	(10)	27	(11)
Discontinuation due to AE	14	(2)	4	(2)
Death	0	(0)	0	(0)
Laboratory abnormalities, ≥2%				
Grade 3-4	329	(38)	91	(37)
Hemoglobin	8	(1)	8	(3)
Alanine aminotransferase (ALT)	75	(9)	28	(11)
Aspartate aminotransferase (AST)	32	(4)	16	(7)
Amylase	29	(3)	10	(4)
Creatinine kinase	31	(4)	7	(3)
γ-glutamyl transferase (GGT)	5	(<1)	8	(3)
Low-density lipoprotein (LDL) cholesterol (fasting)	60	(7)	2	(<1)
Urine erythrocytes	83	(10)	24	(11)
Urine glucose	46	(5)	6	(2)

Study 108 & 110

Safety: Change in $eGFR_{CG}$ & Proteinuria Markers over 144 Weeks

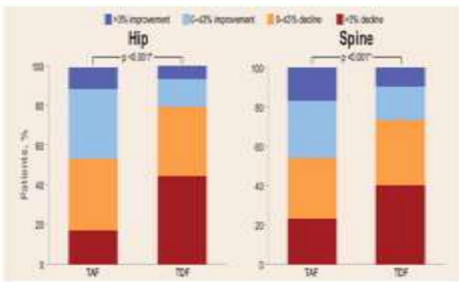
Study 108 & 110

Safety: CKD Stages* at Baseline and Week 144 by $EGFR_{CG}$

		Baseline, n (%)						
		TAF (n=866)			TDF (n=252)			P-value*
		Stage 1	Stage 2	Stages 3-5**	Stage 1	Stage 2	Stages 3-5**	
Week 144	Stage 1	534 (93)	47 (21)	0	125 (78)	5 (13)	0	
	Stage 2	40 (7)	117 (67)	1 (50)	35 (22)	29 (73)	1 (50)	<0.001
	Stages 3-5**	0	10 (6)	1 (50)	0	6 (15)	1 (50)	
	Missing	68	22	1	38	11	1	

Study 108 & 110

Safety: Shifts in BMD From Baseline to Week 144



Study 108 & 110

TAF Demonstrated Potent Viral Suppression and ALT Normalization With Improved Safety in CHB Patients

- In treatment-naive and -experienced HBeAg- and HBeAg+ patients with chronic HBV, VEMLIDY® treatment for 144 weeks demonstrated power ambiviral efficacy[1]:
  - High and similar rates of viral suppression compared with TDF treatment
  - Higher rates of ALT normalization[1]
- *VEMLIDY® was safe and well tolerated in patients with HBeAg- and HBeAg+ patients*
  - *Grade 3-4 AEs, SAEs, and discontinuation due to AEs were similar to TDF*
- *Less impact on renal and bone safety parameters through week 144*
  - *Continued improved renal safety profile compared with TDF*
    - *Significantly smaller decreases in eGFR$_{CG}$*
    - *Smaller changes in markers of proximal tubular function*
  - *Continued improved bone safety profile compared with TDF*
    - *Significantly less declines in hip and spine BMD, with improved bone biomarkers*
- *No resistance to VEMLIDY® was detected through week 144*

AE= adverse event; ALT=alanine aminotransferase; BMD=bone mineral density; eGFR$_{CG}$=estimated glomerular filtration rate (Cockcroft-Gault formula); HBeAg=hepatitis B e antigen; HBV=hepatitis B virus.

1. Chan HLY, et al. AASLD The Liver Meeting® 2016; San Francisco, 2016. Abstract 261. 2. Lim YS, et al. APASL 2016; Oral 474.

TRIO Registry (Real-World US Clinical Practice)

Vemlidy Demonstrate Effective in Asian Hepatitis B Patients

94% (200/212) suppression at baseline

- <2K IU/mL (n=200)
- ≥2K IU/mL (n=12)

99% (205/206) suppression after 6+ months TAF

<2K IU/mL (n=200)			≥2K IU/mL (n=12)		
Not assessed (n=6)	<2K IU/mL (n=194)	≥2K IU/mL (n=0)	Not assessed (n=0)	<2K IU/mL (n=11)	≥2K IU/mL (n=1)

TRIO Registry (Real-World US Clinical Practice)

Vemlidy Showed Improvement in ALT Normalization

13% ↑ **17%** ↑

	Baseline to 6-12mths comparison		Baseline to 13-18mths comparison	
Normal ALT	Paired Baseline	Result between 6-12mths	Paired Baseline	Result between 13-18mths
%	73%	86%	70%	87%
n/N	135/185	160/185	88/126	109/126
	p=0.002		p=0.001	

TRIO Registry (Real-World US Clinical Practice)

Vemlidy Showed Improvement in eGFR

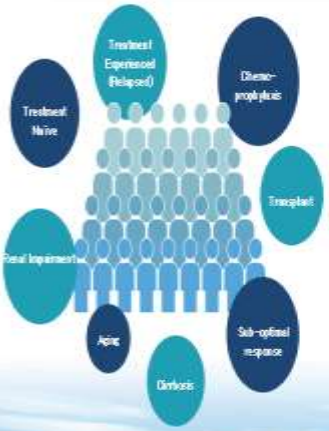
- **Mean eGFR increased 4% after 6mths of TAF treatment**

eGFR mL/min Mean (SD)	Paired Baseline	Results between 6-12mths	Absolute (%) difference 6-12mths
All Patients	86.5 (18.9) n=179	90.1 (18.5) n=179	3.7 (4.2%) p<0.001
Baseline <60 mL/min	48.7 (7.8) n=18	56.1 (12.1) n=18	7.4 (15.1%) p<0.001
Baseline ≥60 mL/min	90.5 (14.6) n=161	93.9 (14.9) n=161	3.3 (3.6%) p<0.001

- **Mean eGFR increased 5% after 12mths of TAF treatment**

eGFR mL/min Mean (SD)	Paired Baseline	Results between 13-18mths	Absolute (%) difference 13-18mths
All Patients	86.2 (17) n=120	90.6 (16.4) n=120	4.4 (5.1%) p<0.001
Baseline <60 mL/min	53.6 (5.7) n=9	63.3 (13.8) n=9	9.7 (18.1) p=0.041
Baseline ≥60 mL/min	88.8 (14.7) n=111	92.8 (14.5) n=111	4 (4.4%) p<0.001

Careful Considerations Needed to be Made for a Broad Patient Population We Face in Our Clinic



Efficacy Factors

- Robust DNA Suppression
- No Drug Resistance
- High ALT Normalization

Safety and Adherence Factors

- Good Safety
- Less Dose Adjustment
- High Patient Adherence

Expert Opinion

High Adherence with Simple Dosing

- No Dose Adjustment
- Administration With Low Food Restriction
- High Adherence[1]

1. Chan HLY, et al. Abstract. Baltimore] 2015;54:a1225.

Dosage Adjustment of NUCs Based On the Renal Function of CHB Patients

Renal Function eGFR (mL/min/1.73 m²)	ETV (0.5 mg)	TDF (300 mg)	TAF (25 mg)
≥50	√ 0.5 mg every day	√ 300 mg every day	√ 25 mg every day
30–49	√ 0.5 mg every 48 hours	√ 300 mg every 48 hours	√ 25 mg every day
15–29	√ 0.5 mg every 72 to 96 hours	√ 300 mg every 72 to 96 hours	√ 25 mg every day
<15 (on Hemodialysis)	√ 0.5 mg every 7 days or after approximately 12 hours of dialysis	√ 300 mg every 7 days or after approximately 12 hours of dialysis	√ 25 mg every day (after dialysis)
<15 (not on Hemodialysis)	√ 0.5 mg every 7 to 10 days	√ 300 mg every 7 to 10 days	

TFDA approved product information for ETV, TDF, and TAF

Clinical Goals of CHB Treatment

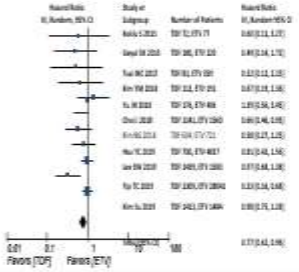
EASL The Home of Hepatology

AASLD

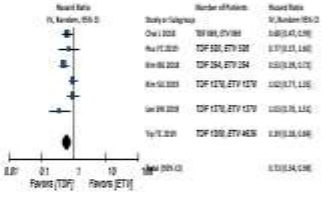
1. Terrault NA, et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance.
2. EASL. J Hepatol. 2017 Aug;67(2):370-398.
3. Sarin SK, et al. Hepatol Int. 2016 Jan;10(1):1-98.
4. Chen RN, et al. Taiwan Consensus Statement on the Management of Chronic Hepatitis B. J Formos Med Assoc. 2018 Jan;117:1-31.

TDF vs ETV on Risk of HCC in Patients with CHB in Meta-Analysis in Favour of TDF

Forest plot of pooled HR for HCC between TDF and ETV



Forest plot of pooled HR for HCC between TDF and ETV in PSM cohorts



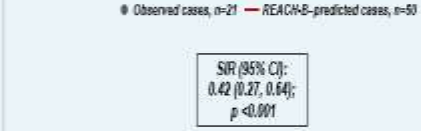
Study 108 & 110 – Impact of TAF or TDF on HCC

Result: Observed vs Predicted Cases of HCC (All Cases)

Treatment Demonstrated Less Onset of HCC vs Predictor

- Two Phase 3, randomized, DB, active-controlled trials (global and China cohorts)

Study 108 (N=578): HBeAg-negative patients & Study 110 (N=1053): HBeAg-positive patients

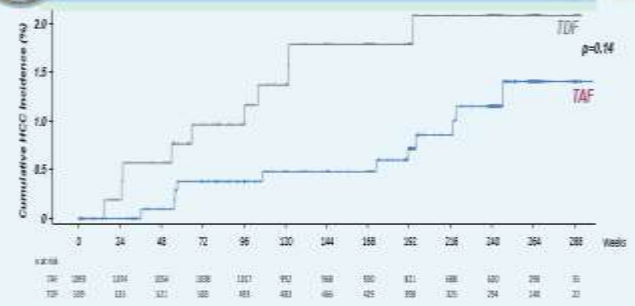


SIR (95% CI): 0.42 (0.27, 0.64); p <0.001

Lim YS, et al. AASLD 2019; 154

Study 108 & 110 – Impact of TAF or TDF on HCC

Results: HCC Incidence and Onset



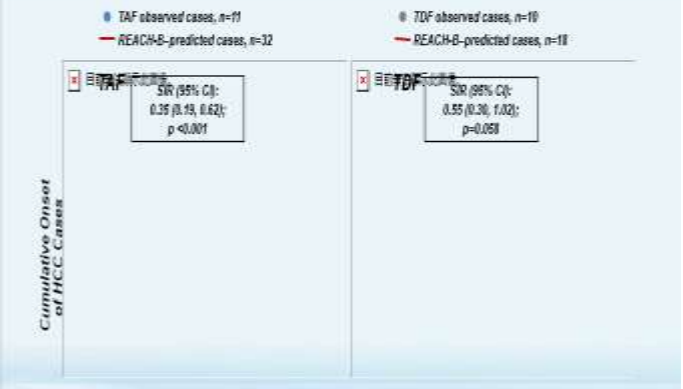
	TAF, n=1035	TDF, n=539	Total, N=1532
HCC cases, n (%)	11 (1.0)	10 (1.9)	21 (1.3)
Double-blind phase, n (%)	5 (0.5)	6 (1.1)	11 (0.7)
Open-label TAF phase, n (%)	6 (0.5)	4 (0.7)	10 (0.6)
Median time to HCC onset, wk (Q1, Q3)	179 (96, 217)	81 (26, 122)	104 (55, 195)

Lim YS, et al. AASLD 2019; 154

Study 108 & 110 – Impact of TAF or TDF on HCC

Observed vs Predicted Cases of HCC (By Treatment)

TAF Demonstrated significantly less onset of HCC



Lim YS, et al. AASLD 2019; 154

Benefit Your Treatment Naïve and Relapsed Patients with Vemlidy

- The potent nucleotide analogue with high barrier to resistance, Vemlidy (TAF), is the recommended treatment of choice for all appropriate CHB patients
- Keeping in mind the long-term treatment goal of CHB is HCC reduction, as there may be some differences between NUCs, therefore, clinical consideration for robust efficacy on viral suppression, ALT normalization, no resistance, long-term tolerability is rendered

Starting with the main therapeutic goals of reducing HCC risk in mind for your broad patient population

- Sustained Viral Suppression (Potent, Low resistance, and Safe)
- Enhanced ALT Normalization Rate
- Simple Dosing to Enhance Compliance

C型肝炎防治

• 按一下以新增副標題

最新C肝口服抗病毒藥物
EPCLUSA® (Sofosbuvir/velpatasvir) 宜譜莎

The Features, Attributes and Benefits of Epclusa®
EPCLUSA®宜譜莎的特色,優勢與益處

2030前滅除肝炎
Eliminating Hepatitis by 2030

2016 World Health Organization

Combating HBV and HCV to reach elimination by 2030

Background

HBV and HCV: A heavy burden of mortality that is increasing
In 2013, viral hepatitis was a leading cause of death worldwide (1.46 million deaths, a toll higher than that from HIV, tuberculosis or malaria, and on the increase since 1990)

Combining prevention and treatment to combat hepatitis makes elimination feasible

- ✓ *Prevention needs*
- ✓ *New medicines*
- ✓ *Reaching five service coverage*

WHO 2030 C型肝炎滅除之願景、目標、方法
WHO Hepatitis Elimination Vision, Mission and Service by 2030

Service

Treatment:
- 90% Diagnosis of HCV infected patients
- 80% Eligible HCV patients treated

(Vaccination)

Prevention:
- 100% Blood donation screening

Injection safety
- 90% Use of engineered devices
- Harm reduction

Mission

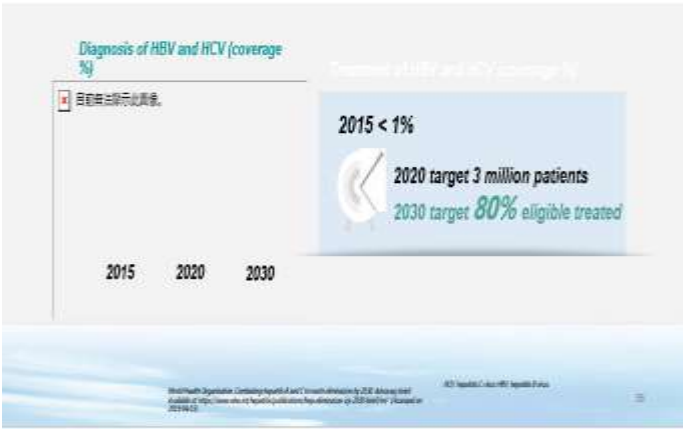
- 65% Reduction in mortality
- 90% reduction in new HCV infection

Vision

2030 HCV Elimination

2030前治療目標
WHO Treatment Goal by 2030

Effective medicines that can save the lives of patients infected HCV is available today.



國內多少C肝病人?

資料來源	收案年代	預估全體anti-HCV陽性人數	預估全體HCV RNA陽性人數†
Chen, Yang, Huang, 2007	1996-2005	423,283	275,134
Yu ML, Yeh ML, Tsai, 2015	1996-2005 為主	745,109	484,321
國民健康暨三高調查[1]	2002	613,189	398,573
C肝肝炎整合各方資料[2]	1996-2016	633,456	411,746
中位數	–	623,323	405,160

干擾素已治療9萬人+目標DAA治療25萬人 = 34萬人 / 40萬人 > 80% WHO 治療目標

台灣C肝政策：國家消除C肝政策綱領（2018 - 2025）

C肝治療實施策略

Joint Efforts of Pharmaceutical Company, HCPs and Patients to Eliminate HCV

台灣C肝治療成果

治療人數

健保給付干擾素療法 93年～107年 **9**萬人 按受治療

健保給付全口服抗病毒藥物 106年1月～108年12月 **7.5**萬人 按受治療

全口服抗病毒藥物治療成效

108年截至108年11月27日止，約4萬5180人接受治療，3萬4353人達服藥後12週之追蹤

完成病毒檢測者之治療成功率為 **98.6%** (mITT)

減除C肝的步驟(評估-選材-監測)

The process to HCV elimination

評估

篩檢 Screening → 回院/轉診/確診 Callback / Transfer/confirmation → 檢測/評估 Pre-test / Consideration

選材

副作用 AE → 交互作用 DDI → 處方治療 Treatment

監測

遵從性 Adherence → 監測 Monitor → 療效 SVR12

Epclusa® 宜譜莎 Sofosbuvir (SOF) / Velpatasvir (VEL)

A single tablet regimen

Sofosbuvir[1] 400 mg — HCV nucleotide analog NS5B polymerase inhibitor

- Potent antiviral activity against HCV GT1-6

Velpatasvir[1-3] 100 mg — HCV NS5A inhibitor

- 2nd-generation NS5A inhibitor with improved resistance profile
- Long half-life of ~13 - 23 h supports once-daily dosing
- No food effect

PI-Free

EPCLUSA®宜譜莎 2018年12月取得衛生福利部藥品許可證

- 適應症：
  - Epclusa適用於治療成人的慢性C型肝炎病毒(HCV)基因型1、2、3、4、5或6之感染症。
- 用法用量：
  - Epclusa的建議劑量為每日一次隨食物或不隨食物口服一錠。
- 肝功能不全：
  - 對輕度、中度或重度肝功能不全(CPT A、B或C級)的患者，並不須調整Epclusa的劑量。曾針對併有CPT B級肝硬化的患者評估過Epclusa的安全性與療效，但尚未對併有CPT C級肝硬化的患者進行過這方面的評估。
- 腎功能不全：
  - 對輕度或中度腎功能不全的患者，並不須調整Epclusa的劑量。目前尚未針對重度腎功能不全(估計腎絲球體過濾率eGFR<30毫升/分鐘/1.73米²)或患有須接受血液透析治療之末期腎病(ESRD)的患者評估過Epclusa的安全性與療效。

病患族群[a]	療法與療程
未曾接受治療與曾經接受治療，未併有肝硬化的患者及併有代償性肝硬化的患者	Epclusa 12週
未曾接受治療與曾經接受治療，併有失代償性肝硬化的患者	Epclusa + ribavirin 12週

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1 Basic Introduction

2 Pan-Genotypic

3 Pan-Fibrotic

4 PI-Free

Table of contents

1 Basic Introduction

2 Pan-Genotypic

3 Pan-Fibrotic

4 PI-Free

Epclusa® 宜譜莎 Sofosbuvir (SOF) / Velpatasvir (VEL)

Prescribing information in Taiwan

Indication

Adult patients* with chronic HCV
Genotypes 1, 2, 3, 4, 5 or 6
infection

* Treatment-naïve, treatment-experienced, co-infected with HIV or post-liver transplant.

Pan-Genotypic

Regimen

Epclusa® 12 weeks

Patients **without** cirrhosis
or **with** compensated
cirrhosis

Epclusa® + RBV 12 weeks

Patients with
decompensated
cirrhosis

Pan-Fibrotic

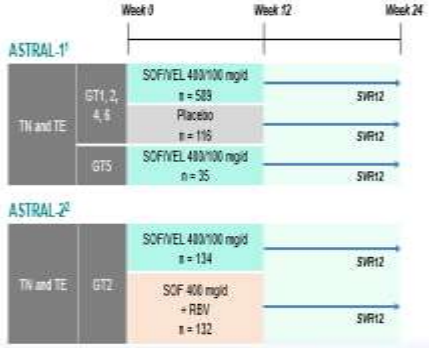
Table of contents

PI, protease inhibitor.

Epclusa® 宜譜莎在基因型1-6的第三期人體試驗

Phase III Trials: Epclusa® in Patients with HCV GT1-6

Study design



Epclusa® 宜譜莎在基因型1-6的第三期人體試驗

Phase III Trials: Epclusa® in Patients with HCV GT1-6

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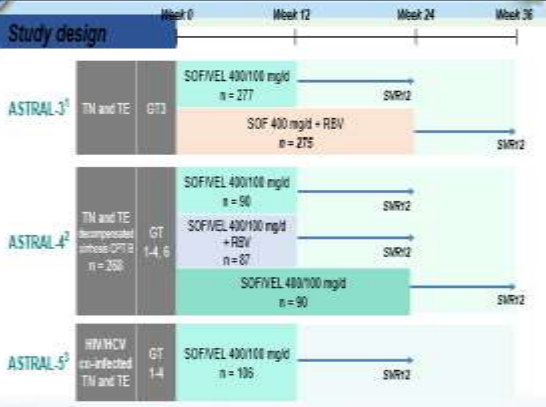
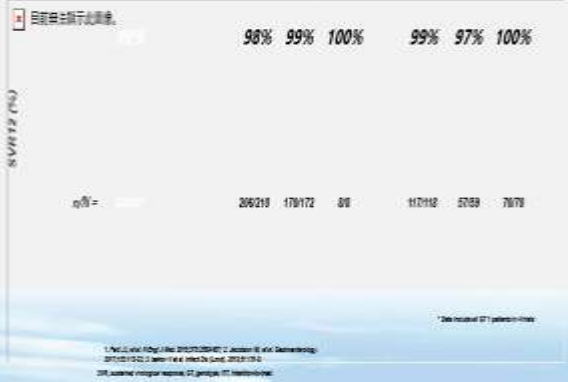


Epclusa® 宜譜莎12週療程臨床試驗資料: 在基因型1顯示高療效

Epclusa® for 12 Weeks Resulted in High SVR12 Rates in GT1a/1b Patients[1-3]

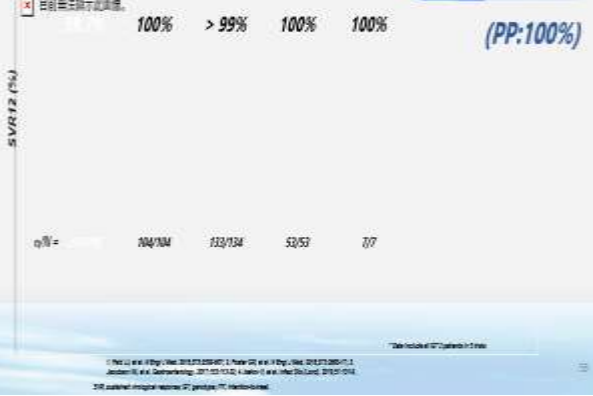
GT1 Overall SVR12* 99% (PP:99%)



Epclusa® 宜譜莎12週療程臨床試驗資料: 在基因型2顯示高療效

Epclusa® for 12 Weeks Resulted in High SVR12 Rates in GT2 Patients[1-4]

GT2 Overall SVR12* 99.7%




Epclusa®宜譜莎12週療程臨床試驗資料:
在基因型3顯示高療效
Epclusa® for 12 Weeks Resulted in High SVR12 Rates in GT3 Patients[1,2]
GT3
Overall SVR12*
96%
(PP:97%)
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95%
97%
96%
97%
SVR12 (%)
n/N =
264/277
86/89
105/109
33/34


泛基因型DAA之效果可能會受第三型之不同抗藥株影響
The efficacy of pan-genotypic DAAs might be impacted by GT 3 RASs
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SVR12
Population =
Resistance analysis in patients with genotype 1-6 HCV infection treated with sofosbuvir/velpatasvir in the phase III studies


Epclusa®宜譜莎真實世界資料:在基因型3顯示高療效
Epclusa® ± RBV achieve high SVR12 for GT3 HCV patients in Real World Data
German ifi Institute
100%
GECCO cohort
100%
TRIO: USA Real World Cohort GT3/F4
98%
TRIO Real World Cohort
97%
EPCLUSA 宜譜莎
NAVIGATORE Lombardia
98%
Italian RWD, 2018 AASLD
97%
98%
12 RWD in 7 countries


Epclusa®宜譜莎12週療程臨床試驗資料:
在基因型4顯示高療效
Epclusa® for 12 Weeks Resulted in High SVR12 Rates in GT4 Patients[1,2]
GT4
Overall SVR12*
99%
(PP:99%)
目前無法顯示此圖像。
100%
98%
SVR12 (%)
n/N =
116/116
56/57


Epclusa®宜譜莎12週療程臨床試驗資料:
在基因型5,6均顯示高療效
Epclusa® for 12 Weeks Resulted in High SVR12 Rates in GT5 & 6 Patients[1,2]
GT5
97%
(PP:100%)
GT6
Overall SVR12*
100%
(PP:100%)
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SVR12 (%)
n/N =
ASTRAL-1 (ITT)
100%
100%
41/41
9/9


Epclusa®宜譜莎12週療程義大利真實世界資料:
在1-5基因型均顯示高療效
Real-World Studies: Epclusa® for 12 Weeks Resulted in High SVR12 Rates
Real-world evidence in Italy
Prospective analysis of a representative Italian cohort involving TN and TE patients (n = 474) with chronic HCV GT1-5 infection.
Efficacy of SOF + VEL antiviral therapy (PP): A, by HCV GT ; B, according to different clinical characteristics
A 目前無法顯示此圖像。
B 目前無法顯示此圖像。
GT1-5
SVR12
99.2%

Short Summary of Pan-Genotypic

Clinical trials

Overall SVR12* 99%

	GT1	GT2	GT3	GT4	GT5	GT6
ITT	SVR12* 99%	SVR12* 99.7%	SVR12* 96%	SVR12* 99%	SVR12* 97%	SVR12* 100%
PP	SVR12* 99%	SVR12* 100%	SVR12* 97%	SVR12* 99%	SVR12 100%	SVR12* 100%

Real-world evidence (PP)

GT1	GT2	GT3	GT4	GT5	Overall
SVR12 99.6%	SVR12 97.6%	SVR12 98.8%	SVR12 100%	SVR12 100%	SVR12 99.2%

Pan-Genotypic

* Data include patients from several trials

EPCLUSA® 宜譜莎在"泛基因型"的特色與優勢

Epclusa® Features and Attributes for Pan-Genotypic

Pan-Genotypic

GT1-GT6 均有高SVR12

- 不需要考慮基因型
- 避免基因檢測錯誤
- 避免未知的混合基因型

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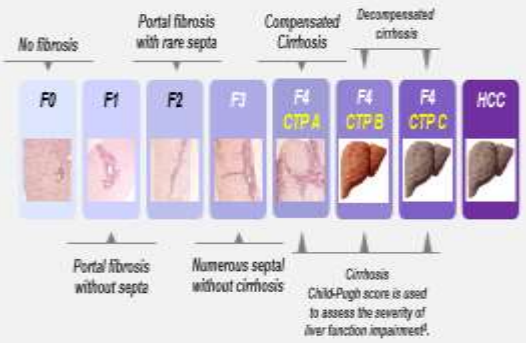
PI, protease inhibitor.

METAVIR計分系統:肝臟纖維化評估與分級

METAVIR Scoring System: Evaluation and Staging of Liver Fibrosis

Using METAVIR scoring system to assess the degree of liver fibrosis[1,2]:



CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma.

Epclusa® 宜譜莎併用雷巴威林 在非代償性肝硬化病患顯示高療效

Epclusa® + RBV Achieved High SVR Rates in GT1-4 Patients with Decompensated Cirrhosis

F4 ASTRAL-4

267 patients with HCV GT1-6 infection and decompensated cirrhosis (F4, CTP B)*

SVR12 rates by GTs: Epclusa® + RBV group

CTP B F4 Overall SVR12 94% (PP:96%)

SOF/VEL+RBV for 12 Weeks in Patients with CPT-C Decompensated Cirrhosis

Flamm, EASL, 2019, THU-178

Phase 2, single-arm, open-label study in patients with any GT and CTP score of 10–12

Baseline Demographics

	N=32
Male, n (%)	26 (81)
Age, mean (range)	55 (39–77)
White, n (%)	18 (56)
GT 1/2/3, %	56/16/22
Mean HCV RNA, log10 (SD)	5.2 (1.0)
HCV RNA ≥800,000, n (%)	9 (28)
CTP class, n (%)	
B (7–9)	9 (28)
C (10–15)	23 (72)
MELD score, n (%)	
10–15	13 (41)
16–20	17 (53)
21–25	2 (6)

*RBV 600 mg, titration to ≤1000–1200mg

7 had no FU-12 assessment due to investigator discretion (n=1) and death (n=6); all unrelated to study drugs

Safety

	N=32
Any AE	31 (97)
Grade 3-4 AE	11 (34)*
Serious AE	17 (53)*
AE leading to D/C	2 (6)*
Death	8 (25)*
Grade 3 Lab Abnormalities	11 (34)
Low lymphocytes	4 (13)
Low platelets	4 (13)
Hyperbilirubinemia	6 (19)
Hyperuricemia	5 (16)
Grade 4 Lab Abnormalities	7 (22)
Hyperbilirubinemia	5 (16)

*Unrelated to treatment; †Grade 4 sepsis and Grade 4 respiratory distress followed by probable sepsis, both resulting in death

Epclusa®宣諾莎12週療程在F3/F4纖維化病患的療效

Epclusa® for 12 weeks in Patients with F3 / F4 Fibrosis

F3/4 Retrospective analysis of ASTRAL-1,2,3

Epclusa® for 12 weeks

501 patients with HCV GT1-6 infection and advanced fibrosis (F3) or compensated cirrhosis (F4)

SVR12 rates, overall and by fibrosis status (ITT)

F3/4 Overall SVR12 98%

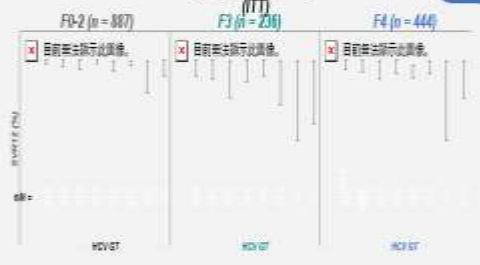
Epclusa®宣諾莎在泛纖維化病患顯示高療效

Epclusa® is Highly Effective Across All GTs Regardless of Degree of Fibrosis

F0-4 Retrospective analysis of ASTRAL-1,2,3 and POLARIS-2,3

F0-4 Overall SVR12 98%

SVR12 rates (%), by GTs and degrees of fibrosis (ITT)



Epclusa®宣諾莎在義大利真實世界不論肝硬化均顯示高療效

Epclusa® is Highly Effective in Italian Patients Regardless of Cirrhosis

Regional registry in Italy

Epclusa® for 12 weeks*

1102 patients with HCV GT1-4, 6 infection and with/without cirrhosis

SVR 12 rates, overall and by FIB-4 index (ITT)

F0-4 Overall SVR12 >98%

Real World study to say about the Epclusa® is highly effective regardless of cirrhosis status.

*In 92.6% of patients; others received Epclusa® for 24 weeks with ribavirin.

Epclusa®宣諾莎在基因型第三型不論肝硬化均顯示高療效

Epclusa® ± RBV Achieved High SVR Rates in GT3 Patients Regardless of Cirrhosis

Prospective multicenter cohort study in Germany (GECCO)

139 patients with HCV GT3 infection with/without cirrhosis (FibroScan > 12.5 KPa or APRI > 2)

SVR4/12 rates, overall and cirrhosis (PP)

F0-4 Overall SVR4/12 100%

0 patients discontinued due to AEs.

No unexpected side effects.

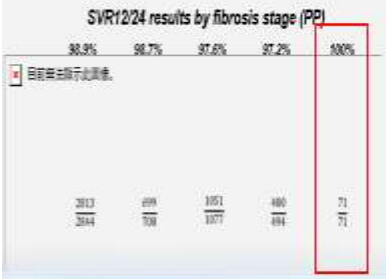
Epclusa®宣諾莎歐美真實世界大量病患資料:在所有基因型不論肝硬化均顯示高療效

Epclusa® Achieved High SVR12 Rates in GT1-6 Patients Regardless of Cirrhosis

12 cohorts study in 7 countries across EU, North-America and Canada*

5541 patients with HCV GT1-6 infection with/without cirrhosis

SVR12/24 results by fibrosis stage (PP)



F0-4 Overall SVR12 98.5%

High efficacy of Epclusa® in all fibrosis stages regardless of fibrosis stage

Epclusa®宣諾莎美國真實世界資料:在所有基因型不論肝硬化均顯示高療效

Epclusa® Achieved High SVR Rates in GT1-6 Patients Regardless of Cirrhosis

Real-world evidence form the TRIO network in USA

Patients with HCV GT1-6 who initiated Epclusa®

SVR12 rates: Epclusa® group (PP)

F0-4 Overall SVR12 98%

High SVR was achieved with Epclusa® in GT1-6 regardless of cirrhosis status.

Short Summary of Pan-Fibrotic

Retrospective analysis of ASTRAL and POLARIS (ITT)

With decompensated cirrhosis

Without cirrhosis or with compensated cirrhosis

F4 94% (PP:96%)

F3-4 98%

F0-4 98%

High SVR12 rates across all GTs regardless of degree of fibrosis.

Real-world evidence (PP)

Without cirrhosis or with compensated cirrhosis

F0-4 >98%

F0-4 100%

F0-4 98.5%

F0-4 98%

Highly effective regardless of cirrhosis status.

Pan-Fibrotic

ASTRAL-4: SOF/VEL ± RBV in HCV Patients with Decompensated Liver Disease

EPCLUSA®治療前至治療後12週纖維化改變

MELD Score Change from Baseline to Follow Up Week 12

EPCLUSA®宜諾莎葉物特性

唯有EPCLUSA可以治療之病人族群

	GT1	GT2	GT3	GT4	GT5	GT6
無肝硬化或代償性肝硬化	Other DAA EPCLUSA	Other DAA EPCLUSA	Other DAA EPCLUSA	Other DAA EPCLUSA	Other DAA EPCLUSA	Other DAA EPCLUSA
失代償性肝硬化	Other DAA EPCLUSA	EPCLUSA	EPCLUSA	EPCLUSA	EPCLUSA	EPCLUSA

EPCLUSA®宜諾莎在"泛纖維化"的特色與優勢

Epclusa Features and Attributes for Pan-Fibrotic

Pan-Fibrotic

F0-F4 都具有高SVR12

- 唯一泛纖維化之泛基因型DAA
- 防止纖維化檢測錯誤導致處方錯誤
- 防止纖維化進展導致處方錯誤

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PI, protease inhibitor.

EPCLUSA 宜諾莎的安全性資料

Safety Profile of Epclusa®

Retrospective integrated safety analysis of data from ASTRAL-1, -2, and -3

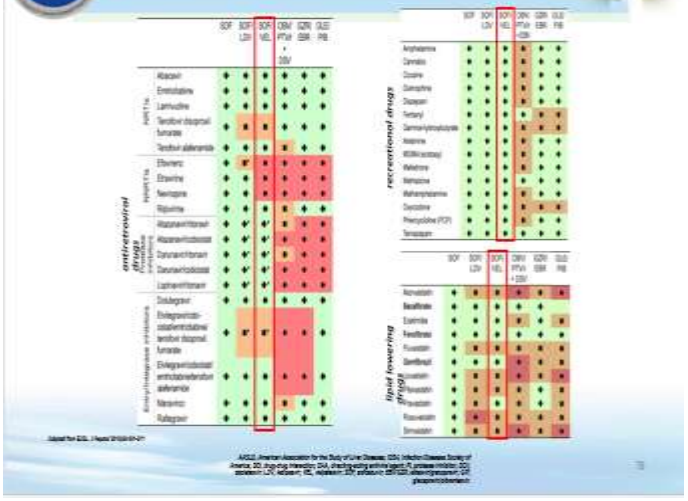
Patients, n (%)	SOF/VEL (N = 1,035)	Placebo (N = 318)
Headache	296 (29)	70 (22)
Fatigue	217 (21)	70 (22)
Nausea	130 (13)	53 (17)
Insomnia	97 (9)	31 (10)
Nasopharyngitis	131 (13)	52 (16)
Cough	57 (6)	15 (5)
Irritability	49 (5)	15 (5)
Pruritis	53 (5)	14 (4)
Dyspepsia	53 (5)	15 (5)

HCV Genotype 1,2,4,5,6

Event	Placebo (n = 116)	SOF/VEL (n = 624)
	No. of patients (%)	
Serious adverse event*	3	15 (2)
Any adverse event	80 (77)	465 (75)

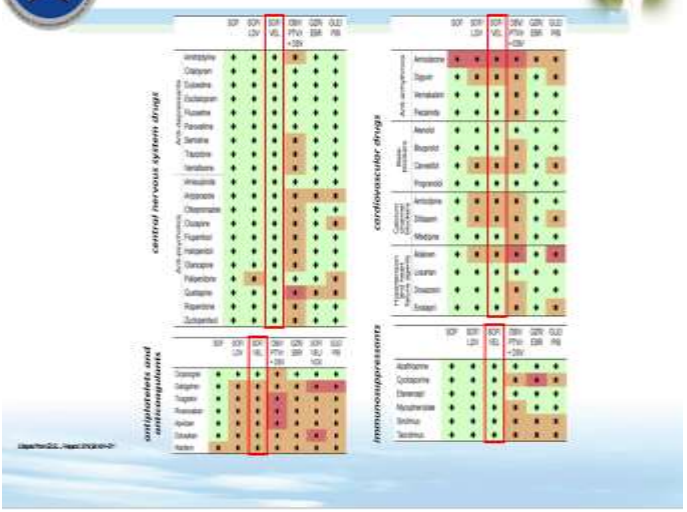
在EASL準則各種DAA與HIV藥物/娛樂性用藥/降血脂藥物交互作用

DAAs DDI with ARV/Recreational/Lipid Lowering Drugs According to EASL Guideline



在EASL準則中各種DAA與中樞神經/心血管/抗凝血/免疫抑制劑藥物之交互作用

DAAs DDI with CNS/Cardiovascular/Anticoagulant/Immunosuppressant Drugs According to EASL Guideline



EPCLUSA®宜譜莎 has Minimal Drug-Drug Interaction with other commonly prescribed drugs

EPCLUSA®宜譜莎在"無蛋白酶抑制劑"的特色與優勢

Epclusa Features, Attributes for PI-free

EPCLUSA®宜譜莎

A Simple and Important Step to eliminate HCV in Taiwan

- Unique mechanism of action: First-in-class nucleotide analog NS5B polymerase inhibitor, and 2nd-generation NS5A inhibitor with improved resistance profile
  - Pan-genotypic
  - Pan-fibrotic
  - PI-Free

- **Pan-Genotype :** EPCLUSA® has been shown to have high SVR~99% in GT1,2,4,5,6 and SVR 95% in GT3.
- **Pan- Fibrotic :** EPCLUSA® treatment provides better hepatic safety and high SVR rates. Epclusa+RBV achieve high SVR for patients with decompensated cirrhosis.
- **PI-free regimen:** EPCLUSA® has minimal DDI concern. Safety and tolerability are confirmed and without hepatic safety concern.
- **Fixed duration :** EPCLUSA® provide fixed 12 weeks of treatment to all patients regardless of HCV genotypes and treatment history.

EPCLUSA®宜譜莎藥物特性

EPCLUSA帶給醫師及病患的益處

EPCLUSA®宜譜莎

唯一同時具有 Pan-Genotypic , Pan-Fibrotic, PI-Free 三種特性的C型肝炎口服抗病毒藥物

- Pan-Genotypic: 泛基因型：GT1-6 治療方法均相同
  - 未來可能免測基因型，降低檢測費用與時間
  - 可降低基因型判斷錯誤之風險
- Pan-Fibrotic: 泛纖維化：所有纖維化等級均可治療
  - 代償性肝病未來可能免測纖維化狀態，降低纖維化檢測之費用與時間
  - 或降低治療中纖維化變化之風險
  - 或降低纖維化檢測錯誤之風險
- PI-Free: 不含蛋白酶抑制劑
  - 可降低藥物交互作用(DDI)發生之風險
  - 降低肝功能變化顧慮

中華民國中央軍事院校校友總會祝您身體健康