PF3009 Gastrointestinal, Hepatic and Endocrine Systems

2017 / 2018

From Bench to Bedside – Drug Integration

Poster Preparation and Presentation

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One of the components of the continuous assessment for module PF3009 is to design your own poster and present the poster to staff members of the School of Pharmacy.

Each poster will focus on a drug used in the treatment of a gastrointestinal, hepatic or endocrine condition.

The poster preparation and presentation is a team-based exercise where each team comprises of four students. The teams and drug assignments can be found at the end of this document.

DACLATASVIR (IN A DA-CLASS-TASVIR OF ITS OWN)

School of Pharmacy University College Cork

UCC University College Cork, Ireland

School of Pharmacy , Cavanagh Pharmacy Building Room UG06 University College Cork

Type of hepatitis C	Treatment recommended by NICE
If your hepatitis C has not been treated before	
1, without cirrhosis	Daclatasvir plus sofosbuvir only for people with significant fibrosis.
4	Daclatasvir plus peginterferon alfa and ribavirin only for people with significant fibrosis or cirrhosis.
If your hepatitis C has been treated before	
1 or 4 without cirrhosis	Daclatasvir plus sofosbuvir only for people with significant fibrosis.
4	Daclatasvir plus peginterferon alfa and ribavirin only for people with significant fibrosis or cirrhosis.

If significant cirrhosis/fibrosis : treatment 24 weeks; otherwise 12 week treatment recommended

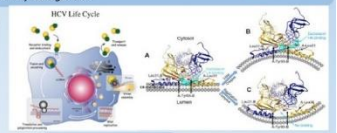
Daklinza (daklatasvir)

St Johns Wort
Carbamazepine
Phosphenytoin
Oxcarbazepine
Phenobarbital
Phenytoin
Primidone
Rifampicin

NS5A inhibitor

Daclatasvir is a direct acting antiviral agent for the treatment of Hepatitis C. The mechanism of action is not fully understood. It is an inhibitor of NS5A, a multifunctional phosphoprotein that is essential for HCV RNA replication complex and required for virion assembly.

HCV Life Cycle



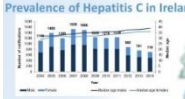
NS5A inhibitors have no enzyme activity but interact with various host proteins including phosphatidylinositol 4-kinase III, a host lipid kinase that is required for HCV replication. Daclatasvir shows low picomolar activity for NS5A from a broad range of HCV genotypes and prevents RNA binding.

NS5A inhibitors interfere with the accumulation of phosphatidylinositol 4-phosphate in the membranous web. Membranous web PI4P is produced in HCV- infected cells, by PI4KIII, that is specifically recruited and activated by the interaction with NS5A. The interaction of these antiviral agents might also interfere with the recruitment and/or activation of PI4KIII by NS5A. NS5A inhibitors show exceptional potency but present a low barrier to resistance.

Goal of treatment with Daclatasvir in Combination Therapy:

The endpoint of treatment is a sustained virological response (no detectable virus 12 weeks post treatment) or **SVR12**. An SVR24 and a negative HCV RNA at 24 weeks be considered virologic cure.

Prevalence of Hepatitis C in Ireland



DACLATASVIR

Combination Medication:
Take Daklatasvir with Sofosbuvir or with peg interferon alpha and ribavirin. You should **not** take Daclatasvir by itself.

IFN-FREE THERAPY

Dose:
Adult : 60mg once daily PO. Available in 30mg, 60mg, 90mg tablet. Not indicated for children.

Cost
The average cost of daclatasvir plus sofosbuvir is $60,000 for a 12-week course and 119.000 for a 24-week course.
HIGH TECH SCHEME

Side Effects:
- Headache
- Tiredness
- Anaemia
- Nausea

May experience side effects related to combination medications also

Lifestyle Advice :
Hepatitis C patients advised to eat a healthy balanced diet. Ideally, anybody with inflammation of the liver should not drink alcohol.

Warning:
Daclatasvir should **not** be used during **pregnancy** or in women of childbearing potential not using contraception.
Use of highly effective contraception should be continued for **5 weeks** after completion of therapy

Daclatasvir Dihydrochloride	
Molecular Weight	811.806 g/mol
Solubility	Freely soluble (>700 mg/mL)
logP	4.18
pKa (Strongest Acidic)	11.15
pKa (Strongest Basic)	6.09
Rule of Five	Yes

Tablet Core

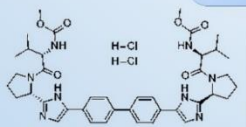
Anhydrous lactose
Microcrystalline cellulose
Croscarmellose sodium
Silicon dioxide (E551)
Mg stearate 1

Tablet film-coat: Hypromellose, Titanium dioxide (E171), Indigo carmine Al lake, Yellow iron oxide (E172), Macrogol 400

Synthesis

Synthesised in three main steps using three commercially available well defined starting materials:
- Alkylation and formation of the imidazole ring
- Coupling reaction
- Formation of the hydrochloride salt

Symmetric, dimeric high molecular weight dimer by design; may not be a critical requirement for productive interactions with NS5A



Four stereocenters (1,1', 2, 2;) in the S configuration
Do not epimerize

N-2 = thermodynamically most stable neat crystalline dihydrochloride salts polymorph and is the only form produced

- Tablet form is readily absorbed,
- Peak plasma conc. **1-2hrs.**
- Daclatasvir Cmax, AUC, and Cmin increases proportionally to dose. Steady state achieved after 4/7 od administration
- Administration of 60mg tab after a high fat meal decreased **Cmax and AUC**, compared with fasting conditions.
- Light meal, resulted in no reduction in daclatasvir exposure.

- Protein binding is ~ 99%, independent of dose.
- Administration of 60 mg tab orally followed by 100 µg IV, **Vdss=47 L**
- **Actively** transported by OCT1 transporters
- **Passively** transported into hepatocytes.
- Daclatasvir **inhibits P-gp, OATP 1B1 and BCRP.** In vitro daclatasvir is an inhibitor of renal uptake transporters, OAT1 and 3, and OCT2, (no clinical effects on substrates of these transporters)

Absorption | Distribution | Metabolism | Excretion

- The liver is the major eliminating organ for daclatasvir. **88%** of total PO single dose recovered in feaces and **6.6%** excreted in the urine.
- Daclatasvir unbound AUC 18-51% higher for patients with impaired **CrCl (15-60 ml/min)** end-stage renal disease had a further increased of AUC relative to normal renal function patients.
- **T1/2 ~ 12-15hrs**

CYP3A4 is the major isoform responsible for the metabolism of Daclatasvir.

- No metabolites circulate at levels **>5%** of the original concentration.
- The Cmax and AUC of total daclatasvir (free and protein-bound drug) are lower in subjects with hepatic impairment

References
Daklinza European Medicines Agency Assessment report. (weblink of pdf file) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003768/WC500172849.pdf
Daklinza Summary of Product Characteristics, BMS (weblink of PDF file) http://www.medicines.ie/medicine/16168/SPC/Daklinza/
Daklinza® Irish Patient Information Leaflet. BMS (weblink of PDF file) http://www.medicines.ie/medicine/16167/XPIL/Daklinza/
GOTTE, M. & FELD, J. J. 2016. Direct-acting antiviral agents for hepatitis C: structural and mechanistic insights. *Nat Rev Gastroenterol Hepatol.* 13, 338-51.
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WISHART, D. S., KNOX, C., GUO, A. C., SHRIVASTAVA, S., HASSANALI, M., STOTHARD, P., CHANG, Z. & WOOLSEY, J. 2006. DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res.* 34, D668-72.

School of Pharmacy University College Cork

Sofosbuvir (So-foscinating!)

UCC University College Cork, Ireland Coláiste na hOllscoile Corcaigh

References
1. *Sofosbuvir* Assessment Report, EMA (EMA/CHMP/608774/2013)
2. Chi A, Butkovich A. Sofosbuvir: A New Oral Once-Daily Agent for The Treatment of Hepatitis C Virus Infection. *Pharmacy and Therapeutics.* 2014;39(5):345-352.
3. Sofia, Michael J.; et al. Discovery of a β-d-2′-Deoxy-2′-α-fluoro-2′-β-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus. *Journal of Medicinal Chemistry* 2010 53 (19), 7202-7218
4. Iyengar S, Tay Teo K, Vogler S, Beyer P, Wiktor S, et al. (2016) Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLOS Medicine 13(5): e1002032. doi: 10.1371/journal.pmed.1002032
5. World Health Organization Hepatitis C Epidemiology http://www.who.int/mediacentre/factsheets/fs164/en/
6. Lawitz E et al Sofosbuvir for previously untreated chronic hepatitis C infection 2013.
7. Bhatia, Harmeet Kaur et al. "Sofosbuvir: A Novel Treatment Option for Chronic Hepatitis C Infection." *Journal of Pharmacology & Pharmacotherapeutics* 5.4 (2014): 278–284. *PMC*. Web. 29 Mar. 2017.
8. Hepatitis C Taxation In India - Why not just Order Hepatitis C Drugs Online? FixHepC.com .

Sofosbuvir (Sovaldi®) should never be administered as monotherapy
Used in combination with other agents ribavirin (RBV)+ peginterferon alfa (PEG) for Hep C treatment.
The tablets should be swallowed whole **with food**. Tablets should not be chewed or crushed due to **bitter taste** of active substance (film coated)[1]
FISSION trial demonstrated a greater efficacy of sofosbuvir&RBV vs RBV&PEG in treating naive patients. 449 patients received either treatment or control. Results showed that only 1 patient on treatment had detectable viral load by week 12 vs 18 in control[6]
Interactions : Pg-P inducers, anti-coagulants, anti-arrythmics, anti-convulsants
SEs Anaemia, Insomnia, Depression, Headache, Nausea & vomiting[2]
Dose: 400mg OD

HCV is a member of the **Flaviviridae** family which has 6 genotypes.
The **ssRNA(+)** genome encodes a single polyprotein that is processed by host and viral proteases into a number of structural and non-structural proteins essential for HCV virulence.

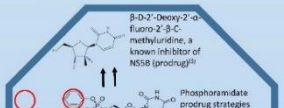
HCV affects 130- 150 million people worldwide and causes 700'000 deaths worldwide annually.
Antiviral medication can cure up to 90% of cases[5]

Sofosbuvir is a **Direct Acting Antiviral (DAA)**
It is a pan-genotypic inhibitor of the HCV NS5B RNA dependent RNA polymerase[2]
It acts as a nucleotide **prodrug** that undergoes intracellular metabolism to form the pharmacologically **active uridine analogue triphosphate.**
1) Intracellular **hydrolytic prodrug cleavage** catalysed by enzymes including carboxylesterase 1 to form monophosphate analogue.
2) Conversion of the monophosphate form to the active triphosphate catalysed by nucleotide kinases[7]

Clinical | The Virus | How it works | Cost | SAR | Pharmacokinetics | Synthesis | Formulation

1 X GS1 = 400 X = 30 years supply

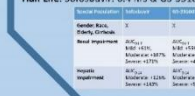
The price of **12 weeks** treatment with Sofosbuvir 400mg daily is **$84,000** (2014)[4,8]
Sofosbuvir and Developing countries
- In 2014 Gilead announced that it would seek **generic licencing** agreements to produce Sofosbuvir in 91 developing countries (54% of HCV infected populations) and that it would sell a product in India for $300 per course of treatment
Signed licences with generic manufacturers by Sept 2015.
Massive influx of Hep C patients seeking treatment in India[8]



- Series of structural analogues with different R1, R2 & R3 groups were synthetized and analysed in cell culture
  - Alanine amino acid = most efficacy
  - C-hex ester = best efficacy but cytotoxic
  - Ph phosphate ester = increased Cmax & AUC

Absorption: [Peak plasma] ~0.5- 2 hour post dose
Standardised high fat meal slowed the rate but increased the extent of absorption. Little effect on the peak concentration
- GS-331007 not altered by a high fat meal

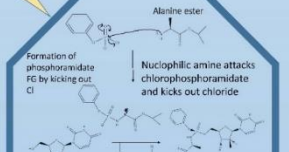
Distribution: ~85% plasma protein bound independent of drug concentration over the range of 1 -20 µg/mL
Metabolism: Extensively metabolised in the liver to form active Nucleoside analogue triphosphate GS-461203
Elimination: Mostly recovered as GS-331007 (78%) – and Sofosbuvir (3.5%) in urine – 80% of po dose
Half Life: Sofosbuvir: 0.4 hrs & GS-331007: 27hrs[1,2]

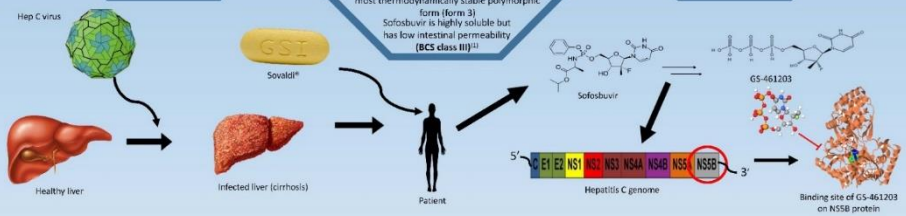


Available as Harvoni® (Sofosbuvir and Ledipasvir) & Sovaldi® (Sofosbuvir only)
Sovaldi® (IR)

Tablet Core	Film Coating
Mannitol	Polyvinyl alcohol
Microcrystalline cellulose	Titanium dioxide
Croscarmellose Sodium	Macrogol 3350
Colloidal anhydrous silica	Talc
Magnesium Stearate	Yellow iron oxide

Magnesium stearate obtained exclusively from vegetable sources – important for religious reasons in some countries with high HCV infection rates.
Blend → Mill → Dry granulate → Compress → Film Coat
API is a crystalline solid manufactured as the most thermodynamically stable polymorphic form (form 3)
Sofosbuvir is highly soluble but has low intestinal permeability **(BCS class III)**[11]





Poster Assessment

The poster component (30 marks) is one-half of the total continuous assessment marks (60 marks) for PF3009.

Marking:

Poster Day:

- Team based mark – assessors
  - Poster design
  - Poster content
  - Communication of the team with an assessor

In addition to a single overall mark being awarded to the team for their poster preparation and presentation as described above, this mark will be adjusted and personalised to each member of the team based upon the observations and scores of other team members. A software programme called CATME (https://info.catme.org/) will be used to gather observations and scores for each team member within a team. The programme will allow each member of a team to score all of the other team members within their team under a number of headings including

- how well each member contributed to the task
- their ability to work as a member of a team
- communication skills, etc.

www.catme.org

The CATME programme allows team members to score and provide comments concerning their team members in a confidential manner so that I will only have access to the information. Team members should be honest in the scores they give and professional in the comments they provide concerning their team members efforts and contributions. The scores provided for each team member will produce a numerical factor that will be multiplied by the team mark for the poster/presentation, resulting in the generation of a mark specific for each individual for the team which reflects both the team and individual team member efforts.

CATME
SMARTER Teamwork

Individual student mark = (team mark) x (CATME team member factor)

www.catme.org

You should receive an email from CATME telling you that the survey is open and asking you to log in.

Open the link that CATME sent you in the email.

Once you do this, you must type in as your name your UCC email address.

You must then create and enter your own personal password into CATME. Choose whichever password you wish.

If you ignored the initial CATME message you can still access CATME through the main CATME webpage (www.catme.org) . Enter your email address into the login screen and click “Forgot Password”. You will then receive another email from CATME to create your password.

Once you log in, you will be prompted to complete the survey with the introductory statement below:

www.catme.org

"*Thank you for participating in this survey concerning the PF3009 Team Poster design, content and presentation. The CATME Peer Evaluation is a confidential means of providing me with honest and professional feedback both on yourself and your team members concerning your experiences from the PF3009 Poster Continuous Assessment component.*

There are nine sections to this questionnaire.

Sections 2 - 6 concern the following headings: Contributing to Work, Interacting with Team mates, Keeping Team on Track, Expecting Quality, Having Knowledge/Skills.

For each of these sections, please click the category for yourself and your team member next to the behaviour that most closely describes how that team member behaved during the poster design, preparation and presentation.

For Section 7 (Team Conflict) and 8 (Team Cohesiveness) please appropriately rank the statements within each section by choosing a category from the dropdown menus to the right of the statements. Sections 7 and 8 comments relate to the team overall. You cannot provide individual feedback of team members in Sections 7 and 8.

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CATME
Peer Evaluation

Help
Logout

Instructions | **Contribution (2 of 9)** | Interaction

Contributing to the Team's Work

<< Back | Next >>

				Description of Rating
○	○	○	○	• Does more or higher-quality work than expected. • Makes important contributions that improve the team's work. • Helps teammates who are having difficulty completing their work.
○	○	○	○	Demonstrates behaviors described immediately above and below.
○	○	○	○	• Completes a fair share of the team's work with acceptable quality. • Keeps commitments and completes assignments on time. • Helps teammates who are having difficulty when it is easy or important.
○	○	○	○	Demonstrates behaviors described immediately above and below.
○	○	○	○	• Does not do a fair share of the team's work. Delivers sloppy or incomplete work. • Misses deadlines. Is late, unprepared, or absent for team meetings. • Does not assist teammates. Quits if the work becomes difficult.

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CATME

Peer Evaluation

Help
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Instructions ... Knowledge/Skills **Conflict (7 of 9)** Cohesiveness

Team Conflict

<< Back Next >>

How often do people get angry while working in your group?	
How much conflict of ideas is there in your work group?	
How much conflict is there in your group about task responsibilities?	
How often are there disagreements about who should do what in your work group?	
How much relationship tension is there in your work group?	
How frequently do you have disagreements within your work group about the task of the project you are working on?	
How much emotional conflict is there in your work group?	
How often do people in your work group have conflicting opinions about the project you are working on?	
How often do you disagree about resource allocation in your work group?	

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The final section (Section 9) is the Comments section. Please provide your confidential overall comments in this section, including specific comments about team members or yourself. You need to justify any particular either critical or praise for team members in this section in a professional and honest manner. **Remember, all of your comments are confidential to myself** and will help me to assign specific marks to team members for their poster contributions in addition to a general team poster mark.