Selected Properties of Simeprevir

<table>
<tr><td>Other names</td><td>Galexos®, TMC435, TMC435350</td></tr>
<tr><td>Manufacturer</td><td>Janssen</td></tr>
<tr><td>Pharmacology/ Mechanism of Action</td><td>Simeprevir is a direct-acting antiviral agent (DAA) against the hepatitis C virus. This agent is a specific inhibitor of the HCV NS3/4A protease which is essential for viral replication.</td></tr>
<tr><td>Activity</td><td>Simeprevir inhibits the proteolytic activity of recombinant genotype 1a and 1b HCV protease. Simeprevir has shown in vitro activity against HCV genotype 1a, 1b and 4 using different cell based replicon assays.

The approved indication for simeprevir is for HCV genotype 1 infection only. Simeprevir for the treatment of HCV genotype 4 and HIV co-infection is still under investigation.</td></tr>
<tr><td>Resistance – genotypic</td><td>The activity of simeprevir against HCV NS3/4A protease in HCV genotype 1a and 1b replicons was reduced by the following amino acid substitutions at NS3 protease positions:

F43, Q80, S122, R155, A156 and/or D168

In Phase 2b/3 studies, the baseline prevalence of Q80K was 30% in genotype 1a infected subjects in the US and rarely found in genotype 1b infected patients (0.5%). The presence of HCV genotype 1a Q80K polymorphism resulted in considerably lower sustained virologic response (SVR) rates compared to patients without the Q80K polymorphism. It is recommended to do a baseline determination of Q80K polymorphism prior to treatment initiation.

D168V or A and R155K mutations were usually associated with simeprevir failure and confer a high level resistance to simeprevir, with a fold change in simeprevir 50% effective concentration (EC_{50}) > 50.

Q80K or R, S122R and D168E mutations confer a low-level resistance to simeprevir, with a fold change in EC_{50} between 2 and 50. However, if more than 2 of these mutations are present, simeprevir activity if reduced by more than 50-fold.

Q80G or L, S122G, N or T mutations have no significant effect on the antiviral activity of simeprevir.</td></tr>
<tr><td>Resistance – phenotypic</td><td></td></tr>
<tr><td>Cross-Resistance</td><td>The following table summarizes the overlapping mutations that affect antiviral activity of the 3 available NS3/4A protease inhibitors:
<table>
<tr><th>Simeprevir</th><th>Boceprevir</th><th>Telaprevir</th></tr>
<tr><td></td><td>V36M</td><td>V36A/M</td></tr>
<tr><td>F43</td><td>F43C/S</td><td></td></tr>
<tr><td></td><td>T54A</td><td>T54A/S</td></tr>
<tr><td>R155</td><td>R155G/I/K/M/Q/T</td><td>R155K/T</td></tr>
<tr><td>A156</td><td>A156S/T/V</td><td>A156S/T/V</td></tr>
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<tr><td>Oral Bioavailability</td><td>Simeprevir has good oral bioavailability.</td></tr>
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Effect of Food	There was no significant food effect on the pharmacokinetics of simeprevir when administered as an oral solution. For the Phase IIb capsule formulation, the bioavailability of simeprevir was 19% lower in the fasted state compared with the fed state (i.e., standardized meal of 21 g fat, 67 g carbohydrates and 19 g protein), indicating a lack of significant effect. Food delays the absorption of simeprevir, increasing time to reach maximum plasma concentration by 1 to 1.5 hours, and increases the exposure of simeprevir by about 60%. Phase 3 studies had no specific recommendations with regard to food intake; more than 80% of the patients had taken simeprevir with a meal most of the time during the study period. It is therefore recommended to take simeprevir with food.
Protein Binding	Simeprevir is extensively bound to human plasma proteins (> 99.9%), mainly to albumin and to a lesser extend to alfa-1 acid glycoprotein.
Vd	
Tmax	In clinical studies in healthy subjects who received 100 mg, 200 mg or 400 mg once daily or 200 mg twice daily simeprevir for 5 days, the median Tmax occurred approximately 4 to 6 hours after administration.
Serum T ½	In clinical studies in healthy subjects who received 100 mg, 200 mg or 400 mg once daily or 200 mg twice daily simeprevir for 5 days, the elimination half-life ranged from 10 to 13 hours. In HCV-infected subjects, the elimination half-life of simeprevir was approximately 41 hours after multiple 200 mg once-daily oral dose; steady-state was reached after 7 days of once-daily dosing.
Drug Concentrations	The pharmacokinetics of simeprevir is nonlinear and is mainly associated with the saturation of CYP3A- gut and liver metabolism and saturation of hepatic uptake. In a pooled analysis of Phase 1 studies, intersubject variability of simeprevir plasma concentration after 7 days of 150 mg once-daily oral dosing of simeprevir was high, with a coefficient of variation of 87% for area under the plasma concentration-time curve up to 24 hour post-dose (AUC_{24h}) and 139% for the predose plasma concentration (C_{0h}). Mean AUC_{24h}: 28,860 ng.hr/mL Mean C_{0h}: 602 ng/mL In HCV-infected patients, simeprevir drug exposure was generally 2- to 3-fold higher compared with healthy volunteers. Pharmacokinetic analysis in Phase 3 studies has shown high intersubject variability with a coefficient of variation for the AUC_{24h} and C_{0h} of 111% and 136% respectively. Mean AUC_{24h}: 57,469 ng.hr/mL Mean C_{0h}: 1,936 ng/mL
Minimum target trough concentrations (for wildtype virus)	In an HCV genotype 1b replicon assay, the median EC_{50} and EC90 were 9.4 nM (7.05 ng/mL) and 19 nM (14.25 ng/mL), respectively. The EC_{50} values varied from 3.7 nM to 25 nM in 3 HCV genotype 1b assays; it was 23 nM and 28 nM in 2 HCV genotype 1a replicon assays. The median simeprevir fold change in EC_{50} values against HCV genotype 2, genotype 3 and genotype 4 were 25, 1,014 and 0.3, respectively.

	No relationship was found between simeprevir drug exposure and the SVR in Phase 3 studies.
CSF (% of serum)	
Metabolism	Simeprevir is metabolized primarily by CYP3A. One minor metabolite was observed in plasma and represented about 8% of the unchanged drug. The metabolites of simeprevir are metabolized via 2 pathways: 1) by oxidation on the macrocyclic and/or aromatic moiety and 2) O-demethylation followed by oxidation. No accumulation of metabolites has been observed after multiple-dose administration of simeprevir.
Excretion	Simeprevir is predominantly eliminated in the feces via biliary excretion. Following a single 200 mg oral dose of 14C-simeprevir, 91% and <0.14% of the dose was excreted in feces and urine, respectively, with approximately 31% of the dose as unchanged drug in the feces.
Dosing – Adult	**Simeprevir must not be administered as monotherapy** and should only be prescribed with both peginterferon alfa and ribavirin. The use of simeprevir in interferon-free regimens is under clinical investigation. The recommended dose for simeprevir is one capsule (150 mg) taken orally once a day (every 24 hours) with food. Treatment duration The recommended duration of treatment with simeprevir is 12 weeks in combination with peginterferon alfa and ribavirin followed by peginterferon alfa and ribavirin for a total of 24 to 48 weeks: • In treatment-naïve patients and prior relapsers with all degrees of liver fibrosis, including cirrhosis, simeprevir combined with peginterferon alfa and ribavirin should be administered for the first 12 weeks, followed by peginterferon alfa and ribavirin for a total treatment duration of 24 weeks. • In prior non-responders to interferon or peginterferon and ribavirin therapy, simeprevir in combination with peginterferon alfa and ribavirin is administered for the first 12 weeks followed by peginterferon alfa and ribavirin for a total treatment duration of 48 weeks. Treatment failure In Phase 2b/3 studies, chances of achieving SVR in patients with a HCV RNA ≥ 25 IU/mL at Week 4 and after were extremely low. Therefore, to avoid unnecessary drug exposure and to limit the risk of developing resistance to simeprevir, patients who have a detectable HCV RNA ≥ 25 IU/mL at Week 4, 12 or 24 should discontinue all treatment. This recommendation is applicable to treatment-naïve patients, prior relapsers and prior nonresponders.
Dosing – Pediatric	No data available on pediatric dosing. Interferon-free studies in pediatric patients are planned.
Adjust in Liver Dysfunction	Simeprevir exposures were approximately 2-fold higher in volunteers with moderate hepatic impairment (Child Pugh B) compared to matched healthy

	controls. In subjects with severe hepatic impairment (Child Pugh C), simeprevir exposures were 2-fold higher compared to those with moderate hepatic impairment and 3-fold higher compared to HCV-infected patients with compensated liver disease. No dose adjustments are required in Child Pugh A or B hepatic impairment. Further study in severe (Child Pugh C) hepatic impairment is planned.[1]
Adjust in Renal Failure/ Dialysis	No clinically significant differences in pharmacokinetics were observed in non HCV-infected volunteers with mild, moderate, or severe renal impairment. Dose adjustment of simeprevir is not required in renal dysfunction.
Toxicity	<u>Most common adverse events:</u> Fatigue, headache, influenza-like illness **Note : The incidence of these adverse events were comparable to patients treated with peginterferon alfa and ribavirine only.* <u>Other adverse events reported:</u> Rash, pruritus, photosentivity Dyspnea <u>Laboratory abnormalities:</u> Increased bilirubin level Anemia and neutropenia occurred at similar incidence rates between patients treated with simeprevir and peginterferon alfa and ribavirin and those treated with peginterferon alfa and ribavirin only. <u>Effect of simeprevir on QT interval</u> A study conducted in healthy volunteers evaluated the effect of simeprevir 150 mg and simeprevir 350 mg once daily for 7 days on the QT/QT corrected for heart rate (QTc). The positive control ECG was performed with a single 400 mg dose of moxifloxacin in each subject. There were no clinically relevant changes on the ECG parameters in these subjects.
Pregnancy & Lactation	Because simeprevir is currently approved in combination with peginterferon alfa and ribavirin, the contraindications applicable to those drugs are also applicable to this triple therapy. Therefore, it is currently contraindicated in pregnant women and in men whose female partners are pregnant. In animal model studies, simeprevir had no teratogenicity in mice and rats. When administered at 6-fold its therapeutic exposure, simeprevir was associated with early and late in utero losses in pregnant mice. There was also a significantly decrease in fetal weights and an increase in fetal skeletal variations when the dose administered was four times human exposure. In a rat model study, pregnancy parameters were not affected when exposed to dose similar to that used in the clinic. The rat offspring with in utero or lactation exposure to simeprevir similar to therapeutic dose had a significantly decrease in body weight, delay physical growth and decrease in motor activity. In a rat fertility study, simeprevir showed no effect on fertility at an exposure comparable to that in humans. No studies in pregnant women or lactating women are available.
Drug Interactions	<u>Effect of simeprevir on other drugs' pharmacokinetics</u> Simeprevir is a mild inhibitor of CYP3A. It also inhibits the hepatic uptake

***** See separate Drug Interaction Table.	transporter by organic anion transporting polypeptide (OATP) and the intestinal efflux transporter P-glycoprotein (P-gp). Co-administration of simeprevir with drugs that are primarily metabolized by CYP3A and/or substrates of P-gp and of OATP may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect as well as their adverse events. Drugs with a narrow therapeutic index are more likely to be affected by co-administration of simeprevir. ▪ HMG-CoA reductase inhibitors: Atorvastatin, simvastatin and rosuvastatin, when co-administered with simeprevir, had an increased exposure outside of the bioequivalence upper limit. Adverse events should be monitored. ▪ Immunosuppressants: No clinically significant interaction has been found between simeprevir and cyclosporine and tacrolimus. ▪ Other drugs: o Simeprevir does not seem alter the concentration of warfarin. INR monitoring should still be considered because of high intersubject variability. o Digoxin exposure is increased when co-administered with simeprevir. Monitor for digoxin efficacy and toxicity. Effect of other drugs on simeprevir's pharmacokinetics Simeprevir is primarily metabolized through the CYP3A pathway. Co-administration of simeprevir with moderate and strong inhibitors and inducers of CYP3A may result in altered plasma concentration of simeprevir, resulting in increased toxicity or decreased efficacy of simeprevir. There is presently no dosage adjustment of simeprevir with these drugs; therefore, it is not recommended and contraindicated. • Efavirenz reduces significantly the plasma concentration of simeprevir. • Rifampin reduces significantly the plasma concentration of simeprevir. • Ritonavir increases significantly the plasma concentration of simeprevir. • Erythromycin increases significantly the plasma concentration of simeprevir. Interaction with antiretrovirals In a drug-drug interaction study evaluating the extent of darunavir/ritonavir and simeprevir interaction, the dose of simeprevir was lowered to 50 mg and co-administered with darunavir/ritonavir 800/100 mg once daily. The AUC of simeprevir 50 mg co-administered with darunavir/ritonavir was still 2.6-fold higher than simeprevir 150 mg administered alone. Therefore, it is not recommended to administer simeprevir with any boosted-PIs. • Rilpivirine is considered compatible with simeprevir. • Raltegravir is considered compatible with simeprevir. • Maraviroc is considered compatible with simeprevir. • All NRTIs, including tenofovir disoproxil fumarate, are considered compatible with simeprevir. • Boosted-PIs are not contraindicated with simeprevir because it increases significantly the plasma concentration of simeprevir. • Efavirenz and nevirapine are contraindicated with simeprevir because it reduces significantly the plasma concentration of simeprevir.
Baseline Assessment	Prior to initiating simeprevir treatment combination, the complete blood count with white blood cell differential count, liver function tests, bilirubin level must be evaluated in all patients.

Routine Labs	HCV RNA levels should be monitored at Week 4, 12 and 24, or at end of treatment.
Dosage Forms	150 mg capsule.
Storage	

References:

1. Ouwerkerk-Mahadevan S, Simion A, Spittaels K, et al. Pharmacokinetics of simeprevir (TMC435) in volunteers with moderate or severe hepatic impairment [abstract O_04]. 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 26-27, 2013, Cambridge, MA.
2. Janssen Pharmaceutical Inc. Simeprevir (TMC435) Briefing Document. NDA 205123. October 24, 2013.
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4. Vertex Pharmaceuticals Inc. INCIVEK Product Monograph. Laval, Qc. August 19, 2013.