



Drug Information Bulletin

Drug Information Centre (DIC)

Indian Pharmaceutical Association

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Content

- *Editorial*
- **New Drug: Sofosbuvir with Velpatasvir for hepatitis C**
- **Cipla introduces new drug for pediatric malaria**
- **Study examines demographic-specific data inclusion in device trials**
- **Notice of DCGI regarding self certification of GMP/GLP by manufacturers**

Editorial

In a historical move Government of India has published Medical Devices Rules 2017 on 31st January 2017 which will take effect from 1st January 2018. Medical Devices were not regulated in India till 1989 when three items were notified as Drugs vide GSR 365(E) dtd. 17.03.1989. Thereafter a small number of medical devices are regulated by Drugs and Cosmetics Act & Rules. In the mean time it was revealed that India is dependent on imported medical devices in the extent of 75 percent and Government of India included this industry under "Make in India" initiative. In order to make India self sufficient on manufacturing Medical Devices in India and to ensure quality and efficiency of the same, India has framed its regulation after a long exercise. About one year has been allowed before its implementation so that industry could get sufficient time to be ready to implement it. It has also been notified that medical devices require to print MRP on the packs of Medical Devices from 1st January 2018. The main feature of this rule is partly self regulating and evaluation by third party unlike Drugs and Cosmetics Act and Rules. Government will also categorize all medical devices in to four categories as per the extent of risk like-Class A (Low risk), B (Low moderate risk), C (Moderate high risk) & D (high risk). As per the rule State licensing authority will issue licenses of the class A & B on the basis of submitted documents or third party audit report, whereas Central Licensing Authority will issue licenses to Class a & B after official inspection by Medical Device Officers. Industry experts feel that the said rule require some fine tuning and Medical Device Officers require adequate training.

Hope medical device industry will take this advantage and will make necessary changes in manufacturing technologies and provide adequate qualified manpower as per the rule before 1st January 2018 and Drug Regulatory officers will provide adequate training by the concerned authorities.



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Congratulations !!!

Dr. Rao V.S.V.Vadlamudi for being elected as the President of Commonwealth Pharmacists Association

New Drug: Sofosbuvir with Velpatasvir for hepatitis C

Approved indication: hepatitis C

Eplusa (Gilead)

tablets containing sofosbuvir 400 mg and velpatasvir 100 mg

Australian Medicines Handbook section 5.5

This is a fixed-dose combination tablet indicated for people with hepatitis C genotypes 1–6. In Australia, approximately 50% of all hepatitis C cases are genotype 1 and 35–40% are genotype 3. Sofosbuvir is already available in combination with ledipasvir¹ and can be used concomitantly with daclatasvir,² peginterferon and ribavirin.³ It is an inhibitor of the NS5B RNA polymerase and blocks viral replication. Velpatasvir is a newly approved drug. Like ledipasvir and daclatasvir, it inhibits the NS5A protein which is required for assembly and release of viral particles.

The efficacy of this combination has been investigated in four main trials (ASTRAL 1–4).⁴

⁶The trials enrolled treatment-naïve and treatment-experienced patients with genotypes 1–6. Compensated liver cirrhosis was allowed in all four studies, but those with decompensated liver disease were only included in ASTRAL-4. The primary efficacy measure in the trials was the proportion of patients who achieved a sustained virologic response. This was defined as undetectable viral RNA in a blood test 12 weeks after the end of treatment.

Almost all patients in ASTRAL-1 (99%) had a sustained response to 12 weeks of treatment with sofosbuvir and velpatasvir. This was irrespective of their hepatitis C genotype, cirrhosis status or previous experience with treatment.⁴ No one in the placebo group had a sustained virologic response.

In ASTRAL-2 and ASTRAL-3, sofosbuvir with velpatasvir was compared to treatments for genotype 2 (12 weeks of sofosbuvir plus ribavirin) and genotype 3 infection (24 weeks of sofosbuvir plus ribavirin). Sofosbuvir/velpatasvir was superior to the comparators for both genotypes (see [Table](#)).⁵

ASTRAL-4 only enrolled patients with decompensated cirrhosis (Child-Pugh B) infected with genotypes 1–4 and 6. Overall, sustained response rates to 12 weeks of sofosbuvir/velpatasvir were high (83%) and comparable to sofosbuvir/velpatasvir plus ribavirin (94%) and 24 weeks of sofosbuvir/velpatasvir (86%). However on further analysis of the different genotypes, only 50% of patients (13/26) with genotype 3 responded to 12 or 24 weeks of sofosbuvir/velpatasvir. When ribavirin was added to 12 weeks of sofosbuvir/velpatasvir, 85% (11/13) of people with genotype 3 had a sustained response.⁶

Another trial (ASTRAL-5) enrolled people with genotypes 1–4 who were co-infected with HIV. The overall response rate to 12 weeks of sofosbuvir/velpatasvir was 95%.⁷

In a pooled analysis of ASTRAL 1–3, the most common adverse events in people taking sofosbuvir/velpatasvir were headache (29% of patients), fatigue (21%), nausea (13%) and nasopharyngitis (12%). These occurred at a similar frequency in those receiving placebo in the ASTRAL-1 trial. Anaemia was common in people who received the combination with ribavirin, particularly in patients with decompensated cirrhosis.

Following oral administration, sofosbuvir is absorbed within an hour and velpatasvir within three hours. Absorption of velpatasvir decreases as gastric pH increases therefore antacids should be taken at least four hours before or after sofosbuvir/velpatasvir. H₂ receptor antagonists can be taken at the same time or 12 hours apart.

Proton pump inhibitors, comparable to omeprazole 20 mg, can also be taken at the same time as sofosbuvir/velpatasvir and with food.

Sofosbuvir and velpatasvir are substrates of P-glycoprotein and velpatasvir is a substrate of cytochrome P450 (CYP) 2B6, CYP2C8 and CYP3A4. Potent inducers of these (e.g. carbamazepine, efavirenz, rifampicin, St John's wort), may decrease serum concentrations of one or both drugs in the combination and co-administration is not recommended. Sofosbuvir/velpatasvir may increase concentrations of digoxin, tenofovir and rosuvastatin, and close monitoring and possible dose adjustment of these drugs is recommended. Concomitant amiodarone can cause symptomatic bradycardia and is not recommended.

It is not known if sofosbuvir/velpatasvir is safe for pregnant women as there have been no adequate studies. No fetal effects were found at high doses in animal studies. It is not known if sofosbuvir and velpatasvir are excreted in human milk, but both were found in the milk of lactating rats. There were no observed effects on nursing rat pups.

When this combination is used with ribavirin, prescribers should be aware that ribavirin is teratogenic and toxic to embryos and is contraindicated in pregnant women and male partners of pregnant women. Female patients and female partners of male patients must use contraception during and for six months after the end of ribavirin treatment.

Patients must be screened for current or past hepatitis B (surface antigen, core antibody) before starting sofosbuvir/velpatasvir as hepatitis C treatment can cause reactivation of hepatitis B infection.

This fixed-dose combination of sofosbuvir and velpatasvir was effective in eradicating hepatitis C infections caused by genotypes 1–6. For most patients, the recommended dose is one tablet a day for 12 weeks. In those with genotype 3 infection who have compensated cirrhosis, the addition of ribavirin may be considered. Unlike some of the other direct-acting combination drugs for hepatitis C (e.g. elbasvir/grazoprevir,⁸ paritaprevir/ritonavir/ombitasvir plus dasabuvir⁹), sofosbuvir/velpatasvir can be used in patients with decompensated liver disease. However, ribavirin should be added to

the regimen in these patients. As yet, there are no clinical data for sofosbuvir/velpatasvir in patients with Child-Pugh C cirrhosis or those who have had a liver transplant. This combination is well tolerated but prescribers need to be aware of the numerous drug interactions that can occur.

References:

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7. Wyles D, Bräu N, Kottlilil S, Daar ES, Ruane P, Workowski K, et al. Sofosbuvir and velpatasvir for the treatment of HCV in patients coinfecting with HIV-1: an open-label, phase 3 study [Epub ahead of print]. *Clin Infect Dis* 2017.
8. Elbasvir/grazoprevir for hepatitis C. *Aust Prescr* 2017;40:32-4.
9. Paritaprevir/ritonavir/ombitasvir plus dasabuvir/with ribavirin for chronic hepatitis C. *Aust Prescr* 2016;39:141-3.

Ref. Australian Prescriber

Indian status:

Sofosbuvir 400 mg +Velpatasvir 100 mg Tablet & Bulk have been approved by CDSCO For the treatment of adult patients with -chronic Hepatitis C virus, Genotype 1,2,3,4,5 or 6 infection.-Without cirrhosis or with compensated cirrhosis-With decompensated with chronic for use in combination with Ribavirin on 04.05.2017.

Cipla introduces new drug for pediatric malaria

Cipla teamed with the Medicines for Malaria Venture to promote 100 milligram Artesunate suppositories for treatment of severe malaria in children from six months to six years of age. The objective is to make the medication available in rural Africa and to national community health programs, said Cipla CEO Umang Vohra.

Ref.: [The Economic Times \(India\)](#)

Study examines demographic-specific data inclusion in device trials

A study of 82 trials supporting FDA premarket approval of medical devices in 2015 showed 4% of the studies evaluated product safety and effectiveness by race, while 9% performed analysis by age and 17% by gender. Authors of the study in JAMA Internal Medicine suggest that trial enrollment of minorities, women and the elderly in proportions used by the product's target population could be required through changes to the Medical Device User Fee Amendments.

Ref.: [Mass Device \(Boston\)](#)

File No. 7-5/2016/Misc./041
Directorate General of Health Services
Central Drugs Standard Control Organization
(O/o Drugs Controller General India)

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Date: 09 AUG 2017

NOTICE

Issues related to universal adoption of Good Manufacturing Practices (GMP) by pharmaceutical sector and to explore the possibility of self certification by the pharmaceutical units followed by third party certification followed by detailed audit have been deliberated at the highest level.

In this regard, it may be mentioned that, CDSCO had earlier prepared a detailed checklist for all manufacturing facilities to comply with the requirements of Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP) as specified under Schedule M and Schedule L-1 of the Drugs and Cosmetics Act and Rules there under. The checklist includes an elaborate tool kit for verification of GMP/GLP along with benchmarks based on the concept of rating manufacturing units on the basis of an estimated risk that they may pose to users of medicines. This checklist was devised with a view to ensure that each manufacturing unit carries out self assessment to GMP/GLP compliance.

All drug manufacturers and pharmaceutical associations were requested vide notice no. 7-5/2016/misc/041 dated 23.07.2015 to make self assessment of their manufacturing units as part of their self audit and mandatorily share their reports with State Licensing Authorities and CDSCO. However, CDSCO is yet to receive self inspection reports from the manufacturers.

In view of above, State Drugs Controllers are requested to direct all the drug manufacturers under their jurisdiction to submit the report of self assessment of their units along with self certification stating that they are complying with GMP/GLP requirement as per Drugs and Cosmetic Rules, to your good office and CDSCO by 30.08.2017.


(Dr. G. N. Singh)
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