

## Review Form 1.6

|                          |                                                                  |
|--------------------------|------------------------------------------------------------------|
| Journal Name:            | <a href="#">Journal of Pharmaceutical Research International</a> |
| Manuscript Number:       | Ms_JPRI_76670                                                    |
| Title of the Manuscript: | TECOVIRIMAT – A REVIEW                                           |
| Type of the Article      |                                                                  |

### **General guideline for Peer Review process:**

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<http://peerreviewcentral.com/page/manuscript-withdrawal-policy>)

**Review Form 1.6**

**PART 1: Review Comments**

|                                     | <b>Reviewer's comment</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>Author's comment</b> (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here) |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Compulsory</b> REVISION comments | <p>Abstract:<br/>           Introduction: Smallpox, is an infectious disease, caused by one of the two virus variants, Variola major and Variola minor There is a longstanding concern that smallpox may be used as a bioweapon. Tecovirimat drug efficacy on smallpox conditions needs to be assessed. Methods: Animal and child Pparticipants of children were given the required dosage of Tecovirimat (TPOXX) and addressed the safety measures were addressed. Results: Participants were analysed for the side effects and reaction to the drug. There is statistically significant improvement in the survival relative to placebo when the infected animals were treated with tecovirimat for 14 days. Conclusion: On the basis of efficacy of Tecovirimat on the animal models and also the pharmacokinetic &amp; safety datas in humans, Tecovirimat has been advanced as a treatment of the smallpox in accordance with the FDA Animals Rule.<br/>           Keywords: Tecovirimat; Smallpox; Toxicity.</p> <p>Manuscript Title: TECOVIRIMAT – A REVIEW</p> <p>Manuscript Number: Ms_JPRI_76670</p> <p>Introduction<br/>           Smallpox, is an infectious disease, caused by one of the two virus variants, Variola major and Variola minor. The last naturally occurred ing case was in October, 1977. It is a contagious and fatal infectious disease with 30% of death rates and higher among babies. The World Health Organizztion eradicated the disease globally in 1980. There is a longstanding concern that smallpox may be used as a bioweapon. The US FDA has approved Tecovirimat (TPOXX) for the treatment of smallpox on 13th July, 20181.<br/>           Indications: For the treatment of human smallpox caused by variola virus in adults and pediatrics children weighing approximately about 13 kg.<br/>           Limitations is Safety and efficacy of Tecovirimat efficacy is has not been determined and proved in humans due to because inadequate and well controlled field trials are not feasible. Also ethically inducing the smallpox disease in humans to study the drug's efficacy is unfair1 not justified.<br/>           Mechanism of Action: Tecovirimat selectively targets and inhibits the orthopox virus VP37 envelope proteins. It blocks the interaction with cellular Rab9 GTPase and TIP47 which in turn prevents the formation of egress-competent enveloped virions essential for the cell to cell dissemination of the virus. There are is no naturally occurring resistance to the drug and also tecovirimat has a lower (?) low barrier for resistance. The possibility of resistance could be considered in the patients whosoever fails to respond to the therapy2.<br/>           Dosage: For weight range of 13-25kg 200mg capsule twice daily, 25-40kg 400mg capsule twice daily, &gt;40 kg 600mg capsules twice daily. It should be taken for 14 days.<br/>           Adverse effects:The safety of Tecovirimat was evaluated in 359 healthy adult subjects between the age groups of 18-79 in a Phase III clinical trial. Out of these 359 subjects, 336 subjects received 23 of 28 doses of the 600mg of drug twice daily for 14 days. Most frequently reported side effects were headache and nausea in 12% &amp; 5% of subjects. Less then &lt;2% of subjects discontinued the drug due to abnormal EEG changes, dry mouth, fever &amp; chills, moderate diarrhoea.<br/>           Pharmacokinetics: Absorbed well and reaches peak plasma levels in 4-6 hours. 77-82% protein binding. Metabolised by hydrolysis and excreted through urine and feces. Tecoviriant is a weak inhibitor of CYP2C8 and CYP2C19 and weak inducer of CYP3A43.<br/>           Uses in specific population1:Pregnancy: No adequate and well controlled studies have been conducted in pregnant women. Animal data – Tecoviriant was given to pregnant mice at doses upto 1000mg/kg/day from gestational days 6-15. No embroyofetal toxicities were observed. Similarly, upto 100mg/kg/day were administered to rabbits and no embroyofetal toxicities were noted.<br/>           Lactation: Tecoviriant when given to lactating mice, the drug was present in the milk. So, it has to be considered in administering the drug during lactation.<br/>           Geriatric: No dosage changes hasve to be made for the ages &gt; 65 years.<br/>           Renal and Hepatic impairment: No dosage alteration is needed in case of even severe renal impairment or hepatic impairment.</p> |                                                                                                                                                                                      |

**Review Form 1.6**

|                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|                                                | <p>Nonclinical toxicology: Carcinogenesis–studies have not been conducted for tecovirant regarding carcinogenicity<sup>1</sup>.</p> <p>Fertility: Female mice – No tecovirant effects were observed in the fertility approximately even after giving 24 times higher the recommended human dose. Male mice: Decreased fertility were was observed in male mice along with testicular toxicity Dose is 1000 mg/kg/day, 24 times higher than that of recommended human dosage.</p> <p>Clinical Trials<sup>1</sup>: Tecovirant efficacy is not determined and proved in humans due to because inadequate and well controlled field trials are not feasible. Also ethically inducing the smallpox disease in humans to study the drug’s efficacy is unfair unjustified. Hence effectiveness of Tecovirant in the treatment of smallpox was experimentally established in the well controlled animal efficacy studies of non human primates and rabbits which were infected with orthopoxviruses. Studies were conducted in the cynomolgus macaques and New Zealand white rabbits infected with monkeypox virus and rabbitpox virus. The primary efficacy endpoint was survival for these studies<sup>4</sup>. Cynomolgus macaquea were administered intravenously with 5 x 10<sup>7</sup> plaque-forming units of monkeypox virus. The drug was given orally at a dose of 10mg/kg once daily for 14 days, after 4,5, or 6th day from the exposure to virus. NZW rabbits were administered intradermally with 1000 plaque forming units of rabbitpox virus<sup>5</sup>. Tecovirant was given orally at a dose of 40 mg/kg once daily for 14 days starting from day 4 after exposure. The dose timing of Tecovirant in the above studies were intended to assess efficacy when treatment is initiated after animals have developed clinical signs of disease, specifically dermal pox lesions in cynomolgus macaques, and fever in rabbits. Survival of the animals was monitored by 3-6 times the mean time to death for untreated animals in each model.</p> <p>Results<br/>There is statistically significant improvement in the survival relative to placebo when the infected animals were treated with tecovirant for 14 days.</p> <p>Conclusion:<br/>On the basis of efficacy of Tecovirant on the animal models and also the pharmacokinetic &amp; safety datas in humans, Tecovirant has been advanced as a treatment of the smallpox in accordance with the FDA Animals Rule.</p> <p>Ethical clearance:<br/>Ethical Clearance for this study was got approved from the Institutional Human Ethical Committee (IHEC).</p> <p>Reference:<br/>Riedel S. Smallpox and biological warfare: a disease revisited. Proc (Bayl Univ Med Cent). 2005 Jan;18(1):13-20. doi: 10.1080/08998280.2005.11928026. PMID: 16200143; PMCID: PMC1200695.<br/>Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, Lovejoy C, Meara I, Long P, Hruby DE. Oral tecovirant for the treatment of smallpox. New England Journal of Medicine. 2018 Jul 5;379(1):44-53.<br/>Zhao D, Chen J, Chu M, Long X, Wang J. Pharmacokinetic-Based Drug-Drug Interactions with Anaplastic Lymphoma Kinase Inhibitors: A Review. Drug Des Devel Ther. 2020 Apr 30;14:1663-1681. doi: 10.2147/DDDT.S249098. PMID: 32431491; PMCID: PMC7198400.<br/>Perry MR, Warren R, Merchlinsky M, Houchens C, Rogers JV. Rabbitpox in New Zealand White Rabbits: A Therapeutic Model for Evaluation of Poxvirus Medical Countermeasures Under the FDA Animal Rule. Front Cell Infect Microbiol. 2018 Oct 5;8:356. doi: 10.3389/fcimb.2018.00356. PMID: 30345258; PMCID: PMC6182097.<br/>Jordan R, Leeds JM, Tyavanagimatt S, Hruby DE. Development of ST-246® for Treatment of Poxvirus Infections. Viruses. 2010 Nov;2(11):2409-35. doi: 10.3390/v2112409. Epub 2010 Nov 3. PMID: 21994624; PMCID: PMC3185582.</p> <p>However, I have recommended in the text, corrections in grammar. Otherwise the document reads well.</p> |  |
| <p><b><u>Minor</u></b> REVISION comments</p>   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
| <p><b><u>Optional/General</u></b> comments</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |

**Review Form 1.6**

**PART 2:**

|                                                     | <b>Reviewer's comment</b>                                                    | <b>Author's comment</b> <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i> |
|-----------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Are there ethical issues in this manuscript?</b> | <i>(If yes, Kindly please write down the ethical issues here in details)</i> |                                                                                                                                                                                             |

**Reviewer Details:**

|                                  |                                                   |
|----------------------------------|---------------------------------------------------|
| Name:                            | <b>Larry H. Bernstein</b>                         |
| Department, University & Country | <b>New York Methodist Hospital, Brooklyn, USA</b> |