Review Form 1.6

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<tr>
<th>Journal Name:</th>
<th>Journal of Pharmaceutical Research International</th>
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<tr>
<td>Manuscript Number:</td>
<td>Ms_JPRI_76670</td>
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<tr>
<td>Title of the Manuscript:</td>
<td>TECOVIRIMAT – A REVIEW</td>
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<td>Type of the Article</td>
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**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)
### Compulsory Revision Comments

**Abstract:**

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 participants 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 & safety data in humans, Tecovirimat has been advanced as a treatment of the smallpox in accordance with the FDA Animals Rule.

Keywords: Tecovirimat; Smallpox; Toxicity.

**Manuscript Title:** TECOVIRIMAT – A REVIEW

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**Introduction**
Smallpox is an infectious disease caused by one of the two virus variants, Variola major and Variola minor. The last naturally occurred case was in October, 1977. It is a contagious and fatal infectious disease with 30% death rates and higher among babies. The World Health Organization 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, 2018.

Indications: For the treatment of human smallpox caused by variola virus in adults and pediatrics children weighing approximately about 13 kg.

Limitations: 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 unfair not justified.

**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 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 who have failed to respond to the therapy.

**Dosage:**
For weight range of 13-25kg 200mg capsule twice daily, 25-40kg 400mg capsule twice daily, >40 kg 600mg capsules twice daily. It should be taken for 14 days.

**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% & 5% of subjects. Less than <2% of subjects discontinued the drug due to abnormal EEG changes, dry mouth, fever & chills, moderate diarrhoea.

**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 CYP3A4.

**Uses in specific population:**

- **Pregnancy:** No adequate and well controlled studies have been conducted in pregnant women. Animal data – Tecoviriant was given to pregnant mice at doses up to 1000mg/kg/day from gestational days 6-15. No embryo-fetal toxicities were observed. Similarly, up to 100mg/kg/day were administered to rabbits and no embryo-fetal toxicities were noted.

- **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.

- **Geriatric:** No dosage changes have to be made for the ages > 65 years.

- **Renal and Hepatic impairment:** No dosage alteration is needed in case of even severe renal impairment or hepatic impairment.
Nonclinical toxicology: Carcinogenesis–studies have not been conducted for tecovirinant regarding carcinogenicity1.

Fertility: Female mice – No tecovirinant 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.

Clinical Trials: Tecovirinant 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 Tecovirinant 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 studies4. Cynomolgus macaques were administered intravenously with 5 x 107 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 virus5. Tecovirinant 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 Tecovirinant 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.

Results: There is statistically significant improvement in the survival relative to placebo when the infected animals were treated with tecovirinant for 14 days.

Conclusion: On the basis of efficacy of Tecovirinant on the animal models and also the pharmacokinetic & safety datas in humans, Tecovirnant has been advanced as a treatment of the smallpox in accordance with the FDA Animals Rule.

Ethical clearance: Ethical Clearance for this study was got approved from the Institutional Human Ethical Committee (IHEC).

Reference:


However, I have recommended in the text, corrections in grammar. Otherwise the document reads well.
### PART 2:

<table>
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<tr>
<th>Are there ethical issues in this manuscript?</th>
<th><strong>Reviewer's comment</strong></th>
<th><strong>Author's comment</strong> (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)</th>
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<tr>
<td><strong>(If yes, Kindly please write down the ethical issues here in details)</strong></td>
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**Reviewer Details:**

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<tr>
<th>Name:</th>
<th>Larry H. Bernstein</th>
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<tbody>
<tr>
<td>Department, University &amp; Country</td>
<td>New York Methodist Hospital, Brooklyn, USA</td>
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