

## TECOVIRIMAT – A REVIEW

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### ABSTRACT:

**Introduction:** Smallpox, 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 need to be assessed. **Methods:** Participants of children were given the dosage of Tecovirimat (TPOXX) and addressed the safety measures. 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 datas in humans, Tecovirimat has been advanced as a treatment of the smallpox in accordance with the FDA Animals Rule.

**Keywords:** Tecovirimat; Smallpox; Toxicity.

### INTRODUCTION

Smallpox, 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% of death rates and higher among babies. The World Health Organisation 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 13<sup>th</sup> July, 2018<sup>1</sup>.

**Indications:** For the treatment of human smallpox caused by variola virus in adults and pediatrics weighing approximately about 13kg. Limitations is Safety and efficacy of Tecovirimat efficacy is not determined and proved in humans due to 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<sup>1</sup>.

**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 no naturally occurring resistance to the drug and also tecovirimat has a lower barrier for resistance. The possibility of resistance could be considered in the patients whosoever fails to respond to the therapy<sup>2</sup>.

**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. <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<sup>3</sup>.

**Uses in specific population<sup>1</sup>:**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 embryofetal toxicities were observed. Similarly, upto 100mg/kg/day were administered to rabbits and no embryofetal 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 has 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 tecoviriant regarding carcinogenicity<sup>1</sup>.

**Fertility:** Female mice – No tecoviriant effects were observed in the fertility approximately even after giving 24 times higher the recommended human dose. Male mice: Decreased fertility were observed in male mice along with testicular toxicity. Dose is 1000mg/kg/day, 24 times higher than that of recommended human dosage.

**Clinical Trials<sup>1</sup>:**Tecovirimat efficacy is not determined and proved in humans due to 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. Hence effectiveness of Tecovirimat 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  $5 \times 10^7$  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 6<sup>th</sup> day from the exposure to virus. NZW rabbits were administered intradermally with 1000 plaque forming units of rabbitpox virus<sup>5</sup>. Tecovirimat was given orally at a dose of 40mg/kg once daily for 14 days starting from day 4 after exposure. The dose timing of Tecovirimat 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 tecovirimat for 14 days.

## CONCLUSION:

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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 Animal Rule.

#### **ETHICAL CLEARANCE:**

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

#### **REFERENCE:**

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