EU Risk Management Plan for Tecovirimat SIGA (tecovirimat monohydrate)

RMP version to be assessed as part of this application:

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Summary of significant changes in this RMP: RMP Parts IV and Part VI II.C have been updated with respect to post-authorisation efficacy studies.

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QPPV name: Jack O'Reilly

QPPV signature:

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Tecovirimat monohydrate
Pharmacotherapeutic group(s) (ATC Code)	Antiviral for systemic use, other antivirals (J05AX24)
Marketing Authorisation Applicant	Diamond Pharma Services B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Tecovirimat SIGA
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Single chemical, synthetic
	Summary of mode of action: Tecovirimat targets and inhibits the activity of the orthopoxvirus VP37 protein (encoded by a highly conserved gene in all members of the orthopoxvirus genus) and blocks its interaction with cellular Rab9 GTPase and TIP47, which prevents the formation of egress competent enveloped virions necessary for cell to cell and long-range dissemination of virus.
	Important information about its composition: Tecovirimat is a tetracyclic acyl hydrazide compound developed by SIGA Technologies, Inc. It is a white to off-white powder and is classified as BCS Class 2 due to its high permeability and low solubility in solutions of gastric pH range. Tecovirimat has a molecular formula of $C_{19}H_{15}F_3N_2O_3 \cdot H2O$ and a molecular weight of 394.33 g/mol. The chemical name is: N-[(3aR,4R,4aR,5aS,6S,6aS)-3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6 ethenocycloprop[f]isoindol-2(1H)-yl]-4(trifluoromethyl)benzamide monohydrate.
Hyperlink to the Product Information	Section 1.3.1 Product Information
Indication(s) in the EEA	Current: Tecovirimat is indicated for the treatment of the following viral infections in adults and children with body weight at least 13 kg: • Smallpox • Monkeypox • Cowpox

<table>
<tr><td></td><td>Tecovirimat is also indicated to treat complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg.</td></tr>
<tr><td></td><td>Proposed: Not Applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:

Adults and children of at least 13 kg

Recommended dose by body weight

<table><tr><th>Body Weight</th><th>Dosage</th><th>Number of Capsules</th></tr><tr><td>13 kg to less than 25 kg</td><td>200 mg every 12 hours for 14 days</td><td>One Tecovirimat 200 mg capsule</td></tr><tr><td>25 kg to less than 40 kg</td><td>400 mg every 12 hours for 14 days</td><td>Two Tecovirimat 200 mg capsules</td></tr><tr><td>40 kg and above</td><td>600 mg every 12 hours for 14 days</td><td>Three Tecovirimat 200 mg capsules</td></tr></table></td></tr>
<tr><td></td><td>Proposed: Not Applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current: Hard capsules. Each capsule contains tecovirimat monohydrate equivalent to 200 mg tecovirimat.</td></tr>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>Yes</td></tr>
</table>

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication and target population(s)

Indication

Tecovirimat is indicated for the treatment of the following viral infections in adults and children with body weight at least 13 kg:

- Smallpox
- Monkeypox
- Cowpox

Tecovirimat is also indicated to treat complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg.

Incidence/Prevalence:

Smallpox: The last naturally occurring case of smallpox reported in the world was in Somalia in 1977. The last case in the United States was in 1949 and in Europe in 1972 in Yugoslavia. In 1980, the World Health Organisation declared that smallpox had been eradicated. Currently, there is no evidence of naturally occurring smallpox transmission anywhere in the world, i.e., the prevalence rate of smallpox is zero (CDC Emergency Preparedness and Response/Smallpox, 2017; NIAID Topics/Smallpox, 2014; Hussain *et al*, 2018).

Monkeypox: Monkeypox is a rare disease that occurs mostly in central and western Africa. The first outbreak ever reported elsewhere in the world occurred in the United States in 2003. There were 37 confirmed, and 10 probable cases (Reynolds *et al*, 2006). In September 2018, the United Kingdom notified two (2) separate monkeypox cases with recent travel history to Nigeria (ECDC Stockholm, 2018). These are the first cases of monkeypox in humans reported in the European Union (EU). A third case of monkeypox was detected in the UK in a healthcare worker who cared for one of the two first cases (ECDC Stockholm, 2018; https://www.nhs.uk/conditions/monkeypox/). In December 2019, the United Kingdom notified one (1) additional imported case of monkeypox with travel history to Nigeria (ECDC, December 2019). Based on the estimated population of the European Union (EU28) at 511 million (Eurostat, 2018) the current prevalence rate of monkeypox in humans is 7.8×10^{-9} (based on 4/511 million, i.e., approximately zero) per 10,000 persons in the Community.

Cowpox: Cowpox is a rare disease worldwide, with fewer than 200 human cases reported in total. From 1969 to 1993, 54 cases were documented in Europe (Baxby et al., 1994). From then until present day, over 50 cases have been reported in Europe, with occurrences in the following countries (number of cases): France (12); Denmark (2); Finland (2); Netherlands (1); Germany (33); Sweden (1); Austria (2); Norway (1); United Kingdom (3), and Russia (1) (Cowpox Epidemiology in Europe (Post-1993), 2009). The most recent outbreak in 2009, revealed 18 cases of human cowpox in Germany, and 12 cases in Northern and Central France, all possibly related to a pet rodent source from the Czech Republic (ECDC Risk Assessment, 2009). Despite these recent outbreaks in Europe (112 cases), the current prevalence rate of cowpox is less than the statutory threshold in the EU (Levin, 2009; Promed-mail, 2009).

Based on the information cited above, 112 cowpox virus cases have occurred in Europe since 1969, which, is estimated and assessed on the basis of data from the European Union (EU28). This represents a population of approximately 511 million for the EU (Eurostat, 2018).

Thus, the estimated prevalence rate of cowpox infection in humans is 2.2 x 10^{-7} (based on 112/511 million, i.e., approximately zero) per 10,000 persons in the Community.

Vaccinia: Vaccinia virus is the aetiological agent of bovine vaccinia disease that causes occasional human outbreaks. However, it is more commonly known for its use as a smallpox vaccine. Historically, the vaccine has been effective in preventing smallpox infection in 95% of those vaccinated. Routine vaccination of the American public against smallpox with the vaccinia virus-based vaccine was discontinued in 1972 after the disease was eradicated in the US (Smallpox vaccine basics, CDC 2017). In Europe, the vaccine is only used in a very small number of laboratory workers at high risk for orthopoxvirus exposure.

Based on the information cited above, 116 orthopoxvirus cases have occurred in Europe since 1969 (not including vaccinia cases). Based on the estimated population of the European Union (EU28) at 511 million (Eurostat, 2018) the current prevalence rate of orthopoxvirus diseases in humans is 2.3 x 10^{-7} (based on 116/511 million, i.e., approximately zero) per 10,000 persons in the Community.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age

- Smallpox: The age distribution of smallpox mirrors that of the general population, although residual immunity from previous vaccination could potentially decrease disease in the older population. Historically young or old individuals are more susceptible to severe smallpox (Hussain *et al*, 2018).
- Monkeypox: In the African epidemics, 90% of the patients were children younger than 15 years. Among the confirmed cases in the 2003 US outbreak (n = 35), 11 patients were younger than 18 years and 24 were older. Although the highest age-specific incidences and the greatest number of cases occur among persons younger than 15 years, a trend toward increasing incidence among persons aged 15-30 years has been seen in recent years. It has been hypothesised that cessation of smallpox vaccination may be a factor in the increasing incidence in this age group, but this theory fails to account for why the disease has not re-emerged in countries where the disease was seen previously, such as West Africa (Graham *et al*, 2018).
- Cowpox: Human cowpox is a disease of young people, with half of all cases occurring in individuals younger than 18 years. Young people may be at greater risk because of a propensity for close contact with animals, such as cats, or because absence of vaccination for smallpox, which may confer some protection against cowpox (Levin *et al*, 2018).
- Vaccinia: Recipients of vaccinia include military personnel and laboratory workers, and as such would be adults of military/ working age.

Gender

The incidence of poxvirus infections is equal in males and females. Although a study from Australia showed a small bias for vaccinia complications in women, other studies have not confirmed this finding, and the bias may be related to the small numbers of patients studied (Patel *et al*, 2018).

Race

Poxvirus infections have no racial predilection. No known ethnic predilections exist for complications related to vaccinia virus.

The main existing treatment options:

Although no drug has been authorised for use in the treatment of orthopoxvirus disease (smallpox, monkeypox, cowpox and vaccinia) in the EU, methods for treatment are available but do not offer satisfactory resolution of the disease condition. These methods include supportive and symptomatic treatment, passive immunisation in treating certain adverse effects associated with vaccination, and possible disease treatment with a limited number of antiorthopoxviral medications. Neither passive immunisation nor antiviral methods are approved for use for the orthopoxvirus disease treatment indication in the EU.

Supportive and symptomatic treatment

Treatment strategies to target clinical manifestations of orthopoxvirus disease or toxaemia are available. These strategies include supportive therapy such as intravenous fluids, medications for fever or pain and antibiotics for secondary bacterial infection. Treatment strategies for toxaemia are also possible. Toxaemia is largely due to an uncontrolled or inappropriate immune response to infection and manifests as a type of 'septic shock' that can lead to multiple organ failure and death (Levi *et al*, 2004). Thus, modulation of the systemic immune response to infection by the use of activated protein C or inhibitors of the tissue factor pathway (Geisbert *et al*, 2003) could help prevent organ damage caused by vascular leakage and fibrin deposition.

Supportive therapy, while critical for overcoming milder forms of orthopoxvirus disease and complications such as secondary bacterial infections, does not target the infection directly. Treatment strategies for toxaemia are also supportive and have not yet been fully tested in a non-human primate (NHP) model for smallpox.

Passive immunisation

Passive immunisation has been used to treat adverse effects associated with vaccination (CDC MMWR, 2007) or exposure to vaccinia virus in recombinant vaccines for other viral diseases such as rabies (CDC MMWR, 2009). Vaccinia immune globulin (VIG) is currently the only product that is approved in the US for treatment of complications from smallpox vaccination with vaccinia virus and might have therapeutic efficacy in systemic orthopoxvirus infections *caused* by smallpox or monkeypox viruses (Xiao *et al*, 2010).

Passive immunisation is not approved for use, and while it may be beneficial in treating adverse effects associated with vaccination, it has no proven benefit in smallpox treatment, and its efficacy in treatment of monkeypox infections is unknown.

Antiorthopoxviral medications

Concerns over the possible use of variola or other zoonotic orthopoxviruses as biological weapons prompted renewed interest in determining whether any existing licensed medications had anti-pox viral activity (LeDuc *et al*, 2002). In 1999, an Institute of Medicine panel recommended the development of new antiviral drugs against smallpox, especially medications that could be taken by mouth (Fenner *et al*, 1988; Institute of Medicine, 1999). The panel noted the need for a number of drugs with different mechanisms of action that could protect against possible emergence of a drug-resistant virus, initiating efforts to develop and test various antiviral drugs for treatment of orthopoxvirus diseases and vaccination complications (LeDuc *et al*, 2002; Baker *et al*, 2003; Bray and Roy, 2004).

Screening of licensed antiviral medications identified 3 drugs with activity against variola and other orthopoxviruses. None of these drugs described below, has been approved for treatment of orthopoxvirus diseases. While the antiviral compounds have been shown to inhibit orthopoxvirus replication *in vitro*, they are not approved for use, often lack potency and/or are associated with significant adverse effects due to their relative non-specific mechanisms of virus inhibition.

a) Ribavirin (Rebetol®, Ribavirin Teva Pharma B.V, Ribavirin Teva, Ribavirin Mylan) is approved, in combination with interferon, for treatment of hepatitis C virus infection, and is available in an oral formulation. Ribavirin is less active against poxviruses than cidofovir (Baker *et al*, 2003). Studies in animal models of lethal pox viral infection, have shown ribavirin to be minimally protective (Smee and Sidwell, 2003).

b) Adefovir dipivoxil (Hepsera®) is approved for treatment of chronic hepatitis B infection. Adefovir dipivoxil is less active *in vitro* against variola virus than cidofovir; it's *in vivo* efficacy has not been evaluated (Baker *et al*, 2003).

c) Imatinib mesylate (Glivec®, Imatinib Accord, Imatinib Teva, Imatinib Actavis) is approved for treatment of chronic myelogenous leukaemia and has been shown to be partially protective against a low-dose vaccinia virus challenge in mice (Reeves *et al*, 2005). Imatinib mesylate causes side effects, including fluid retention, nausea and vomiting, muscle cramps, fatigue and headache in the majority of treated patients. Treatment was shown to be partially protective against a low-dose vaccinia virus challenge in mice, but there are no reports of activity in other models (Reeves *et al*, 2005).

The first two agents are nucleoside analogues that block viral DNA replication or transcription, and at toxic levels, interfere with the same cellular processes, while the third directly inhibits cellular protein kinases (Reeves *et al*, 2005).

Cidofovir (Vistide®) is another nucleoside analogue which was approved for treatment of cytomegalovirus (CMV)-retinitis in individuals with AIDS (De Clercq, 2002), and shows activity against smallpox virus (Lalezari *et al*, 1997; Quenelle *et al*, 2003). It was only available as an intravenous formulation. However, the marketing authorisation in the EU was withdrawn in 2014 after being in short supply since 2013 due to manufacturing problems.

Cidofovir's use for the treatment of orthopoxvirus diseases was limited due to the route of administration (intravenous) and associated adverse effects (nephrotoxicity) (Lalezari *et al*, 1997). Furthermore, resistant virus variants are common (Smee *et al*, 2002). The development of the orally available derivative Brincidofovir (CMX001) overcame the obstacles of renal toxicity and drug administration. Brincidofovir is not yet approved by the FDA (Melamed *et al*, 2018) or the EMA.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Smallpox: Smallpox is caused by the variola virus, a member of the genus *Orthopoxvirus*. The two predominant variants of variola, major and minor, differ greatly in their mortality rates (30% vs 1%, respectively). Variola major was the predominant endemic strain throughout the world, and by the end of the 18th century, it was responsible for approximately 400,000 deaths a year in Europe. In patients who recovered from the disease, blindness was common, and disfiguring scars were nearly universal.

During the first half of the 20th century, all outbreaks of smallpox in Asia and most in Africa were due to variola major. Variola minor was endemic in some countries in Europe, North America, South America, and many parts of Africa.

Variola major smallpox has four subtypes, as follows:

- Ordinary smallpox: The most common form, which accounts for 90% or more of smallpox cases
- Modified smallpox: A mild form that develops in previously vaccinated persons
- Flat smallpox (malignant smallpox): A severe variety of smallpox in which lesions do not project above the skin surface
- Haemorrhagic smallpox (fulminant smallpox): A rare, very severe, highly fatal variety of smallpox in which haemorrhages develop in the skin and mucous membranes.

Variola minor is less common and much less virulent; it was previously found mainly in South Africa, South America, Europe, and Australia.

Other types of smallpox include the following:

- Variola sine eruptione (variola sine exanthemata): Another less common form of smallpox.
- Pulmonary form of smallpox: Characterised by severe symptoms, cyanosis, and bilateral infiltrates; has been described in individuals with little or no smallpox immunity; the mortality rate of this type is undetermined.
- Pharyngeal form of smallpox: Develops in immunised individuals; this form presents with a spotty enanthem over the soft palate, uvula, and pharynx.
- Influenza-like form of smallpox: Rarely results in a rash.

The pharyngeal and influenza-like forms are relatively mild, usually affect individuals who have been previously immunised, and do not cause mortality (Hussain *et al*, 2018).

Smallpox infections present with acute onset of fever (>38.3°C), malaise, head and body aches, and sometimes vomiting. This phase is followed by a rash characterised by firm, deep-seated vesicles or pustules in the same stage of development. Clinically, the most common rash illness likely to be confused with smallpox is varicella (chickenpox).

A person with smallpox goes through several stages as the disease progresses. Each stage has its own signs and symptoms.

- The incubation period can last anywhere from 7 to 19 days (although the average length is 10 to 14 days).
- The initial symptoms include high fever, head and body aches and sometimes vomiting. This stage lasts anywhere from 2 to 4 days.
- The early rush stage starts as small red spots on the tongue and in the mouth. These spots change into sores that break open and spread large amounts of the virus into the mouth and throat. The person continues to have a fever. Once the sores in the mouth start breaking down, a rash appears on the skin, starting on the face and spreading to the arms and legs, and then to the hands and feet. Usually, it spreads to all parts of the body within 24 hours. As this rash appears, the fever begins to decline, and the person may start to feel better. This stage lasts about 4 days. By the fourth day, the skin sores fill with a thick, opaque fluid and often have a dent in the centre. Once the skin sores fill with fluid, the fever may rise again and remain high until scabs form over the bumps.
- The 'pustular rash and scabs' stage lasts about 10 days. The sores become pustules (sharply raised, usually round and firm to the touch, like peas under the skin). After about 5 days, the

pustules begin to form a crust and then scab. By the end of the second week after the rash appears, most of the sores have scabbed over.

- Scabs fall off, leaving marks on the skin. This stage lasts approximately 6 days. Three weeks after the rash appears, most scabs will have fallen off.
- Four weeks after the rash appears, all scabs should have fallen off. Once all scabs have fallen off, the person is no longer contagious.

Morbidity is commonly associated with smallpox. Most patients (65-80%) recovering from infection have cutaneous scarring, which is made worse if secondary bacterial infections develop during the course of smallpox. Other complications of smallpox included dehydration and orchitis. Encephalitis occurs in 1 in 500 cases. Dermatologic complications of smallpox include formation of furuncles and/or abscesses secondary to bacterial infection, sepsis and pockmarks. Ophthalmologic complications are developed in 10-20% of smallpox patients and include blepharitis, conjunctivitis, corneal ulceration, keratitis and blindness (1% of cases). Orthopaedic complications include arthritis (2% of cases), osteomyelitis variolosa (affecting 2-5% of children) and symmetrical elbow joint involvement. Respiratory complications include pulmonary oedema, pneumonitis and bronchopneumonia (Hussain *et al*, 2018).

Overwhelming toxaemia has been the usual cause of death in smallpox. Variola major infection carries an overall fatality rate of approximately 30% (range, 15-50%) in an unvaccinated population and 3% in a vaccinated population. However, flat smallpox carries a 45.4% mortality rate in patients with discrete lesions who have been immunised. Unimmunised patients with confluent disease have a 99.3% mortality rate. Patients with haemorrhagic smallpox have a mortality rate of more than 96%, regardless of immunisation status.

Variola minor infection is a less common type of smallpox and a much less severe disease, with a death rate of 1% or less.

Congenital smallpox infection results in a stillbirth rate of 35%; 50% of neonates die within their first few days of life (Hussain *et al*, 2018).

Monkeypox: Monkeypox in humans is clinically similar to smallpox but overall is less infectious and less deadly. The symptoms of monkeypox are milder than the symptoms of smallpox. The most reliable clinical sign differentiating monkeypox from smallpox is enlarged lymph nodes (lymphadenopathy) in monkeypox. Lymphadenopathy is not present in smallpox (Graham *et al*, 2018).

The stages and associated symptoms of monkeypox are as follows:

- The incubation period averages 12 days, ranging from 4-20 days.
- In the prodrome or pre-eruptive stage (lasts 1-10 days), fever is commonly the first symptom (usually 38.5-40.5°C). The febrile illness is often accompanied by chills, drenching sweats, severe headache, backache, myalgia, malaise, anorexia, prostration, pharyngitis, shortness of breath, and cough (with or without sputum).
- Lymphadenopathy appears within 2-3 days after the fever.
- In the exanthem (eruptive) stage, most persons develop a rash within 1-10 days after the onset of fever. The rash often starts on the face and then spreads to the rest of the body. Lesions progress through the following stages before falling off: macules, papules, vesicles, pustules, and scabs. The rash persists for 2-4 weeks until all lesions have shed their crusts. Encephalitis with immunoglobulin M found in the cerebrospinal fluid has been reported.

The illness in the US was generally self-limited, with resolution in 2 to 4 weeks depending on the severity of the illness. However, a small subset of patients, most commonly paediatric patients, had a more

severe course, with several patients requiring ICU care. No fatalities were reported in the US and UK outbreaks. African cases have mortality rates of 1-10%, with the highest rates occurring in children and individuals without smallpox vaccination. In general, the prognosis is related to the amount of exposure to the virus, host immune response, comorbidities, vaccination status, and severity of complications. Complications reported from African outbreaks include pitted scars, deforming scars, secondary bacterial infection, bronchopneumonia, respiratory distress, keratitis, corneal ulceration, blindness, septicaemia, and encephalitis. Most patients died of secondary infections (Graham *et al*, 2018).

Cowpox and vaccinia: Human infections with vaccinia, wild vaccinia like viruses, cowpox, and cowpox like viruses are most often self-limited, characterised by localised pustular (and in cowpox, occasionally ulcerative) lesions. Fever and other constitutional symptoms may occur briefly after lesions first appear. Lesions can be painful and can persist for weeks. People who are immunocompromised or who have exfoliative skin conditions (such as eczema or atopic dermatitis) are at higher risk of severe illness or death (CDC, 2017).

The prognosis for patients with cowpox is very good. Human cowpox is usually a self-limiting disease. The host immune response is usually sufficient to control the viral infection, and the only sequelae are scars at the site of the pox lesions. Cowpox patients with underlying skin disorders, such as atopic dermatitis, are at risk for generalised skin infection, resembling eczema herpeticum. Of the eight cases of severe generalised skin infection that have been reported, four of the patients had atopic dermatitis, one had Darier disease, and one had hay fever. There have only been two reported deaths associated with cowpox. One was in a patient with atopic dermatitis and allergic bronchial asthma who was receiving systemic steroids at the time of infection. The patient died from pulmonary embolism however the autopsy failed to demonstrate the role cowpox may have played in the patient's death. The second was in an adolescent renal transplant patient in Finland who developed neck swelling, tonsillitis, and widespread vesico-pustular lesions after exposure to an infected cat. He was found to have cowpox particles in his skin and blood by electron microscopy and polymerase chain reaction. He did not respond to antiviral therapy and died of multiorgan failure (Levin *et al*, 2018).

Most adverse reactions to vaccinia administration involve the skin and central nervous system (CNS) (Patel *et al* 2018). Typically following vaccinia vaccination, a vesicular or pustular skin lesion at the site of inoculation is indicative of a successful vaccination or "take". Forty (40) to 47% of vaccinees report mild pain at the site of inoculation and 2–3% reports the pain as severe. Fever is common after vaccination with 5 to 9% reported above 37.7°C and 3% above 38.8°C. In addition, many vaccinees report a variety of mild systemic complications, including headache, myalgia, chills, nausea and fatigue. Moderate and severe complications of vaccinia vaccination include eczema vaccinatum (in subjects with a history of eczema or atopic dermatitis), generalised vaccinia, vaccinia necrosum (in immunocompromised subjects), myopericarditis and post-vaccinal encephalitis (mostly in children). Moderate to severe complications occur in approximately 1 to 250 individuals per million primary vaccines (Jacobs *et a*l, 2009).

Although complications from vaccinia vaccination are uncommon (75 per million vaccinations, death rate of 1 per million), the outcome depends on the immune status of the individual. In immunocompromised persons, mortality rates from dermal complications (e.g., eczema vaccinatum, vaccinia necrosum) were reported as 10% and nearly 100%, respectively. When patients are treated with vaccinia immune globulin (VIG), the mortality rate is drastically reduced. After 1969, when VIG became available, investigations suggested mortality rates of 1% for eczema vaccinatum and 33% for vaccinia necrosum. Individuals who previously received the vaccine and are undergoing revaccination may be at greater risk for complications than those who are immunologically naive to it. Post-vaccinal encephalitis, characterised as an encephalopathy in children, carries a mortality rate of 25%. This is usually observed in children aged 6 months to 3 years; therefore, vaccination should be postponed until children are older. Adults can experience a milder form of encephalitis characterised by perivascular demyelination.

CNS complications are essentially unheard of after revaccination, are not related to underlying immunosuppression, and do not respond to VIG therapy (Patel *et al* 2018).

Important co-morbidities:

As described under 'Demographics' above, these orthopoxviral conditions may infect anyone in the general population although the very young and elderly are more susceptible to smallpox, whereas for example, monkeypox and cowpox and vaccinia are often diseases of the young. There are thus no specific important co-morbidities although logically, the immunocompromised may be more susceptible to infection. Tecovirimat efficacy may be reduced in immunocompromised patients based on studies demonstrating reduced efficacy in immunocompromised animal models. However, it is not anticipated that there would be an increased risk of adverse events in these patients.

Part II: Module SII - Non-clinical part of the safety specification

The toxicology programme for tecovirimat includes a comprehensive set of non-clinical toxicology studies designed to support the oral administration of tecovirimat in the clinic. The effects of tecovirimat have been evaluated in a non-clinical development programme including GLP-compliant repeat-dose toxicity studies (of up to 13 weeks in duration) in mice and monkeys, a standard battery of *in vitro* and *in vivo* genetic toxicity tests, and a battery of reproductive and developmental toxicity tests including a fertility and early embryonic development study in mice, EFD studies in mice and rabbits, and a prenatal and post-natal development study in mice.

The majority of *in vivo* studies were conducted using the oral (gavage) route of administration, which is the intended clinical route. The drug substance used in the pivotal toxicology studies matches the purity and impurity profile of that used in the human clinical studies.

The use of mice and monkeys as the main repeat-dose toxicity species is supported by pharmacology data as well as PK data. Specifically, early non-clinical evaluations of the PK and safety of tecovirimat in mice, rats, rabbits, dogs, and monkeys have indicated that the rat, rabbit, and dog are not suitable for tecovirimat toxicology evaluation. This is because of data which indicate possible auto induction following repeated administration of tecovirimat, variable bioavailability, and limited PK exposure in rats and rabbits and hyper-sensitivity for electroencephalographic (EEG) and CNS events in dogs. Thus, the mouse and monkey were selected for toxicology evaluations. Both mouse and monkey used in efficacy models further supporting their use for toxicology evaluations.

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings (from Non-clinical Studies)	**Relevance to Human Usage**
Toxicity	
Single-dose Toxicity Pivotal single-dose toxicity studies conducted in mice and monkeys demonstrated that tecovirimat was well tolerated following oral administration of up to 2,000 mg/kg (in both species) which produced high systemic exposures to tecovirimat. In a maximum tolerated dose (MTD) study in dogs, single oral administration of tecovirimat resulted in seizures and mortality at 300 mg/kg/day; however, no apparent seizures or changes in EEG were noted at 100 mg/kg/day. Tecovirimat exposures were higher in male dogs compared to females, which may explain why the CNS signs were observed in male dogs. The dose level of 100 mg/kg in the male dog produced C_{max} and $AUC_{0\text{-}24h}$ values of 5,575 ng/mL and 25,224 h•ng/mL, respectively, and in the female dog produced C_{max} and $AUC_{0\text{-}24h}$ values of 3,825 ng/mL and 14,058 h•ng/mL, respectively.	**Toxicity** Both single-dose and repeat-dose toxicity studies with tecovirimat administered by the oral route to mice and monkeys showed no significant tecovirimat-related findings. The exposures achieved in mice and monkeys were higher than the human clinical exposure (at 600 mg BID dosing for 14 days). The dog appears to be hypersensitive to the tecovirimat-induced CNS side effects as these findings were not seen in any of the other animal species tested with tecovirimat. However, based on these data, the C_{max} value of 5,575 ng/mL is considered to be the maximum allowable exposure level for humans.
Repeat-dose Toxicity	

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
In repeat-dose toxicity studies, there were no significant tecovirimat-related findings in either mice or monkeys administered tecovirimat by the oral route. In mice, oral administration of tecovirimat for 28 days and 3 months resulted in significant increases in relative liver and spleen weights at dose levels of 600 mg/kg/day and above; however, these findings were not considered to be of toxicological significance given that there were no microscopic or clinical chemistry findings and the weight changes were absent in the recovery animals. Due to the lack of tecovirimat-related effects at the highest dose levels in the 28 day and 3-month study, respectively, the no-observed-adverse-effect levels (NOAEL) in the 28 day and 3-month mouse studies were 2,000 and 1,000 mg/kg/day, respectively. The exposures achieved in mice at the 1,000 mg/kg/day dose level in the 3-month study were approximately 21- to 24-fold and 26- to 32-fold over the human clinical exposure (at 600 mg BID dosing for 14 days) for AUC and C_{max} values, respectively. In the monkey, oral administration of tecovirimat for 28 days or 3 months did not result in any test article-related effects at the highest tested dose level of 300 mg/kg/day. Thus, this level was determined to be the NOAEL in male and female monkeys following 28 days and 3 months of oral dosing. The dose of 300 mg/kg/day for 3 months in the monkey produced AUC and C values of 2.5-fold and 2.4-fold over the human exposures, respectively, at a clinical dose of 600 mg BID for 14 days. There is no evidence that tecovirimat causes seizures or pre-seizure changes in the monkey at oral dose levels of up to 300 mg/kg/day for up to 3 months.	
Reproductive and Developmental Toxicity In the reproductive and developmental toxicity studies, oral gavage administration of tecovirimat to male and female mice was not associated with any adverse effects on female fertility, implantation, or early embryonic development at dose levels of 100, 300, or 1,000 mg/kg/day. A significant increase in	**Reproductive and Developmental Toxicity** No embryo-foetal or maternal toxicity was recorded in mice. Although maternal toxicity at highest dose tested was evident in the rabbit study, no embryo-foetal abnormalities were recorded.

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
the number of abnormal sperm was noted in males at 1,000 mg/kg/day, but no adverse effects noted at 100 or 300 mg/kg/day. This increase was not considered to be biologically meaningful. No treatment-related effects were noted at necropsy. In the fertility and early embryonic development study, a significant decrease was noted in the rate of viable foetuses at the high-dose level of 1,000 mg/kg/day; however, this finding was observed in the absence of a significant decrease in the fertility/fecundity rates and was attributed to a single pregnant high-dose female that was included in the calculations for fertility/fecundity indices but was not included in the group of females given a uterine exam on GD 13 (as a definitive GD 13 could not be determined for this animal). There were no other tecovirimat-related effects reported on any fertility parameters. In the EFD studies conducted in mice and rabbits, oral administration of tecovirimat resulted in adverse effects on maternal rabbits when given during the period of organogenesis but no effects on EFD or teratogenicity. Maternal toxicity noted in rabbits receiving 100 mg of tecovirimat/kg/day (the highest dose tested in this species) included mortality (in 9 out of 22 rabbits) and significant decreases in body weight (due to decreases in food consumption). The weight loss impacted the number of live foetuses per doe and increased the post-implantation losses and early resorption levels. The maternal NOAELs were considered to be the highest dose level of 1,000 mg/kg/day in mice and the mid-dose level of 30 mg/kg/day in rabbits while the developmental NOAELs in mice and rabbits were determined to be the highest dose levels of 1,000 and 100 mg/kg/day, respectively. In a pre- and post-natal development study conducted in mice, the oral administration of tecovirimat at 100, 300, or 1,000 mg/kg/day did not result in any adverse effects on pre- or post-natal development. The reproductive and developmental toxicity studies were further supported by a mouse study that showed the oral administration of tecovirimat to	No adequate and well controlled studies in pregnant women were conducted; therefore, there are no human data to establish the presence or absence of tecovirimat associated risk. The background risk of major birth defects and miscarriage for the indicated population is unknown. Tecovirimat orally administered to dams can cross the placenta and also be transferred to offspring through the milk. No adequate and well controlled studies in breast-feeding women were conducted; therefore, there are no human data to establish the presence or absence of tecovirimat associated risk. It is not known whether tecovirimat is excreted in human milk. Decreased fertility due to testicular toxicity was observed in male mice. There are no data on the effect of tecovirimat on female and male reproductive potential in humans.

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
dams can cross the placenta and also be transferred to offspring through the milk.	
Safety Pharmacology *In vitro* and *in vivo* safety pharmacology studies have demonstrated the following: • That tecovirimat, at a concentration of 30 µM (the highest concentration tested), has no inhibitory effect on hERG-mediated potassium currents; • That oral (gavage) administration of tecovirimat was not associated with any significant effects on CV function in monkeys following 28 days of daily dosing at levels of 30, 100, or 300 mg/kg/day; and • That oral (gavage) administration of tecovirimat was not associated with significant effects on respiratory function in mice at dose levels of up to 2,000 mg/kg. In addition, there were no significant cardiovascular effect of the oral administration of tecovirimat on qualitative or quantitative ECG parameters in monkeys administered a single oral dose of tecovirimat up to 2,000 mg/kg, or multiple oral doses of tecovirimat as high as 300 mg/kg up to three months. Only in one study, a 12-day multiple oral dose (300 mg/kg/day) study in monkeys, was there evidence for a mild, transient, possibly tecovirimat-related, prolongation of the QT interval. A GLP-compliant neurobehavioral study in mice demonstrated that the oral (gavage) administration of tecovirimat at single dose levels of 500, 1,000, or 2,000 mg/kg resulted in a slightly lower, but statistically significant, value for general arousal (decreased level of exploratory activity in the open field) in high-dose females, significant decrease in defecation counts in mid- and high-dose animals, and a significant and dose-dependent decrease in body temperature in treated females. While the temperature decreases observed at the low- and mid-dose levels were not considered adverse, the degree of hypothermia observed following administration of the high-dose level of 2,000 mg/kg in females was considered to be a clear adverse event. There were no test article-related	**Safety Pharmacology** *In vitro* and *in vivo* safety pharmacology studies indicate that tecovirimat is not expected to pose a significant CNS, respiratory, or CV risk. Only in one study, a 12-day multiple oral dose (300 mg/kg/day) study in monkeys, was there evidence for a mild, transient, possibly tecovirimat-related, prolongation of the QT interval. However, based on the results of a thorough QTc trial, tecovirimat does not prolong the QT interval to any clinically relevant extent at the anticipated therapeutic exposure. There were no safety alerts for the cardiovascular system, respiratory system, neuromuscular tone/function and sensorimotor function in clinical trials. The decrease in body temperature seen in female mice at a dose of 2,000 mg/kg has not been observed during human studies. The dose of 2,000 mg/kg greatly exceeds the human exposures (AUC) by 28 times.

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
effects on parameters generally indicative of neuromuscular tone/function or on sensorimotor function tests.	
Genotoxicity Tecovirimat was not genotoxic in *in vitro* or *in vivo* assays, including a bacterial reverse mutation assay, a mammalian mutagenicity assay in mouse lymphoma L5178Y/TK$^{\pm}$ cells, and in an *in vivo* mouse micronucleus study.	Tecovirimat did not exhibit genotoxic potential in the studies conducted.
Carcinogenicity Carcinogenicity studies have not been conducted with tecovirimat.	The anticipated duration of administration of tecovirimat is 14 days. As such, according to Guideline CHMP/ICH/140/95, carcinogenicity studies are not required for medicinal products used for short-term therapy where prolonged exposure is unlikely. Although animal carcinogenicity tests have not been performed with tecovirimat, there is no reason to suppose from the chemical structure that the compound is likely to possess significant carcinogenic potential.

In summary, the pharmacology and non-clinical toxicology of tecovirimat supports the clinical use of this compound as an oral treatment of smallpox (variola) virus and other orthopoxviruses. Based on the totality of the data, especially the NOEL dose of 300 mg/kg/day after 90 days in the monkey, tecovirimat demonstrates a suitable clinical safety margin.

Other toxicity-related information or data

Both single-dose and repeat-dose toxicity studies with tecovirimat administered by the oral route to mice and monkeys showed no significant tecovirimat-related findings. The exposures achieved in mice and monkeys were higher than the human clinical exposure (at 600 mg BID dosing for 14 days).

Reproductive and development toxicity studies have shown signs of maternal toxicity at the highest dose of tecovirimat tested in the rabbit, but no embryo-foetal abnormalities were recorded. No embryo-foetal or maternal toxicity was recorded in mice. Tecovirimat orally administered to dams can cross the placenta and also be transferred to offspring through the milk. An increase in abnormal sperm count was observed in male mice at highest dose administered. Toxicity studies in monkeys for 12 days, 28 days, and three months were conducted using juvenile animals (less than 36 months old) and demonstrated no evidence of systemic toxicity at the doses administered. Based in the non-clinical findings, reproductive and development toxicity is a potential risk when administering tecovirimat to these patient populations.

Pregnant and breastfeeding women were not included in the clinical trials with tecovirimat and there are therefore no human data to establish the presence or absence of tecovirimat-associated risk.

The requested indication for the product is: "*Treatment of orthopoxvirus disease (cowpox, monkeypox, smallpox and vaccinia complications) in adults 18 years of age and older and paediatric and adolescent*

patients weighing at least 13 kg." Exposure of healthy paediatric subjects to Tecovirimat with no potential for direct clinical benefit to assess safety is not ethical, and therefore the benefits of treatment must be considered carefully against any potential risks when used in children weighing 13 kg or more. The product is indicated for rare or eradicated diseases and may only be needed in the event of an intentional virus release or complications arising during a mass vaccination campaign. Under such circumstances, the clinician would need to carefully consider on an individual basis whether the potential benefits of treatment of orthopoxvirus infection with tecovirimat outweigh any potential risks if considered for use by pregnant or breastfeeding women and their infants or, for males and females with reproductive potential.

Part II: Module SIII - Clinical trial exposure

In the absence of a significant orthopoxvirus disease burden in the human population, traditional drug development that includes demonstration of efficacy in infected human patients is not possible because adequate and well-controlled field trials have not been feasible and inducing an orthopoxvirus disease in humans to study the drug's efficacy is not ethical. Therefore, efficacy data for tecovirimat are based on studies conducted in animals alone. The pivotal *in vivo* efficacy studies were conducted in Cynomolgus monkeys and rabbits; additional studies were conducted in mouse, prairie dog, and squirrel models. Pharmacokinetics, pharmacodynamics, and safety data are from clinical trials with human subjects.

The safety of tecovirimat in humans, has been established in 12 clinical studies with non-infected human subjects, including subjects with varying degrees of renal and hepatic impairment.

The safety profile of tecovirimat in humans primarily relies on one pivotal Phase 3 study (SIGA-246-008), in which the study population, healthy adult subjects aged 18-79 years, is believed to adequately represent the population for treatment. The results of this study are supported by three (3) three supportive multiple-dose studies (SIGA-246-015, SIGA-246-002, and SIGA-246-004 , and eight (8) supportive single-dose studies (SIGA-246-001, SIGA-246-PO-005, SIGA-246-006, SIGA-246-009, SIGA-246-010, SIGA-246-012, SIGA-246-013, and SIGA-246-018—note that while safety data was derived from the SIGA-246-006 study, drug was not ingested).

The clinical studies that have been conducted with tecovirimat have focused on safety and tolerability evaluations and pharmacokinetics at various dose levels, primarily under fed conditions. Additionally, one of the studies was designed to evaluate the effects of a single supratherapeutic dose of tecovirimat on the QT interval. All the clinical studies with tecovirimat were performed in adults.

No statistical analysis plan (SAP) was developed for review of safety because only study SIGA-246-008 represents the most robust safety data (for the target population for treatment and at the agreed-upon clinical dose of 600 mg twice daily for 14 days).

All human studies were conducted according to Good Clinical Practice (GCP) guidelines.

Overall, the size of the safety database from the pivotal, supportive multiple-dose, and supportive single-dose clinical studies enables adequate, meaningful assessment of the safety and tolerability profile of tecovirimat.

Across all pivotal, supportive multiple-dose, and supportive single-dose studies of tecovirimat, subjects have been exposed to tecovirimat at total daily doses ranging from 250-2000 mg for between 1 and 21 days. In the cases of emergency and Named Patient use, the patients were exposed to tecovirimat at daily doses ranging from 50-1200 mg for between 14 days and approximately 2 months.

Exposure data for the pivotal, supportive multiple-dose, and supportive single-dose studies are summarised below.

Table SIII.1: Duration and dose of exposure

Duration of exposure	**Daily Dose (mg)**										**Total subjects per duration of exposure**
	2000	1000	800	600 (BID)	600	500	400	250	100	200	
1 day	7	64		7	70	8	1	12	12		181
2 days				3	31		11				45
3 days				3			2				5
5 days				4							4
7 days				1							1
8 days				1							1
9 days				1							1
10 days				1	1		1				3
11 days				1							1
12 days				2	2		1				5
13 days				7	1						8
14 days			1	328	41		42	1			413
15 days				78							78
20 days			1				1				2
21 days			6				6	7			19
Total subjects per daily dose	7	64	8	437	146	8	65	8	12	12	**Total subjects** 767
Person time (days)	7	64	160	5912	745	8	849	161	12	12	**Total person time (days)** 7930

BID=Twice daily

Table SIII.2: Age group and gender

Age group	**Subjects**		**Person time**	
	M	F	M	F
Adults (e.g. 18 to 64 years)	379	352		
Elderly people				
65-74 years	12	20		
75-84 years	1	3		
85 + years	0	0		
Total	392	375		

Table SIII.3: Ethnic origin

Ethnic origin	**Subjects**	**Person time**
Hispanic or Latino	164	
Not Hispanic or Latino	602	
Other	1	
Total	**767**	

Table SIII.4: Race

Race	**Subjects**	**Person time**
White	512	
Black	218	
Asian	14	
American Indian or Alaska Native	8	
Native Hawaiian or Other Pacific Islander	3	
Other	12	
Total	**767**	

In addition to the 11 clinical studies with non-infected volunteers, there is clinical experience from six (6) cases of emergency use in the US (from 2007 to 2016) and four (4) cases of Named Patient use in Europe (the first in Finland in 2009 and three (3) further cases during 2019 in Germany and Sweden).

Emergency use in the US:

- A 28-month-old male (10 kg) received tecovirimat orally for 14 days at a dose of 50 mg (2 days), 75 mg (2 days) and 100 mg (10 days) once daily.
- A 20-year-old male received treatment for 73 days with daily oral tecovirimat (400-1200 mg; total of nearly 75 g) and for 68 days with topical tecovirimat (39.7-1110 ng/mL).
- A 37-year-old female received tecovirimat orally for 14 days at a dose of 400 mg once daily.
- A 25-year-old female received tecovirimat orally for 14 days at a dose of 400 mg once daily.
- A 19-year-old male received tecovirimat for two months at a dose of 600 mg twice daily.
- A 26-year-old female received tecovirimat orally for 14 days at a dose of 600 mg twice daily.

Additional details are provided in CTD Modules 2.7.2 Summary of Clinical Pharmacology Studies and 2.7.4 Summary of Clinical Safety.

Named Patient use in Europe:

- A 32-year-old female in Finland received tecovirimat orally for 14 days at a dose of 400 mg once daily for cowpox infection.
- A 32-year-old male in Germany received tecovirimat orally for nine (9) days twice daily (dose not specified) for cowpox infection.
- A 57-year-old female in Sweden received tecovirimat orally for four (4) months at a dose of 600 mg twice daily for cowpox infection. The dose was then increased to 800 mg twice daily. A month later, the dose was again increased to 1000 mg twice daily.
- A 34-year-old female in Germany received tecovirimat orally for seven (7) days at a dose of 400 mg twice daily for orthopoxvirus infection.

Part II: Module SIV - Populations not studied in clinical trials

Children

The safety of tecovirimat in children and adolescents below 18 years of age has not yet been established.

Paediatric subjects have not been studied in clinical trials with tecovirimat. Since tecovirimat has been developed for treatment of rare or eradicated diseases and may only be needed in the event of an intentional virus release or complications arising during a mass vaccination campaign, clinical efficacy studies, especially in paediatrics, cannot be justified.

Subjects age across the tecovirimat clinical safety studies ranged from 18 to 80 years, so safety data are available for young adults.

Therefore, it is proposed that the plan for use in the paediatric age-groups should be based on juvenile non-clinical safety, pharmacokinetic (PK) and efficacy studies, and adult clinical safety studies.

SIGA submitted a Paediatric Investigation Plan (PIP) to the EMA for tecovirimat on 09 September 2019 (EMEA-001205-PIP02-19). Following Day 60 and 90 comments and submission of responses, the 'Opinion of the Paediatric Committee on the agreement of the PIP and a deferral' was issued on 29 May 2020.

Elderly

Elderly subjects have only been studied to a limited degree in clinical trials with tecovirimat.

Analysis of a subset of safety variables based on age was undertaken in two (2) clinical studies of tecovirimat: study SIGA-246-008 and study SIGA-246-004. In study SIGA-246-008, there were no statistically significant effects of age on the incidence of TEAEs when subjects were stratified into four (4) groups (18-30 years, 31-34 years, 46-64 years, and 65-80 years), but when the groups were collapsed into two (2) groups (18-45 years versus 46-80 years), older subjects had a somewhat increased chance of experiencing a TEAE compared to younger subjects (odds ratio of 1.70). In study SIGA-246-004, there were no statistically significant differences in the incidence of TEAEs based on age, regardless of whether subjects were stratified into four (4) groups or two (2) groups.

Together, these results suggest no clinically important effects of age on the safety of tecovirimat.

Pregnant and breastfeeding women

The safety of tecovirimat in pregnant and breastfeeding women has not yet been established.

No clinical studies of tecovirimat in pregnant women have been performed, and there is no clinical experience with tecovirimat in lactating women to know whether tecovirimat is excreted in human breast milk.

Subjects of Different Racial and/or Ethnic Origin

Subjects of different racial and/or ethnic origin have only been studied to a limited degree in clinical trials with tecovirimat.

Racial and/or ethnic origin had no clinically significant effect on the pharmacokinetics of tecovirimat.

Immunocompromised subjects

The safety of tecovirimat in immunocompromised subjects has not yet been established.

No clinical studies of tecovirimat in immunocompromised subjects have been performed. Studies in immunocompromised animal models demonstrated a potential for reduced efficacy, but no increased safety concern.

Subjects with orthopoxvirus diseases

The safety of tecovirimat in patients with orthopoxvirus diseases has not yet been established.

Patients with the target conditions (smallpox, monkeypox, cowpox and vaccinia complications) were not included in the clinical development programme. Only very limited data is available from six (6) cases of emergency use in the US and four (4) cases of Named Patient use in Europe.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria in the pivotal Phase 3 study (SIGA-246-008):

Exclusion criteria	**Reasons for exclusion**	**Is it considered to be included as missing information?**	**Rationale for not including as missing information**
Pregnant or breast-feeding or planning pregnancy	Maternal toxicity at highest dose tested was evident in a rabbit study, no embryo-foetal abnormalities were recorded. Tecovirimat orally administered to dams can cross the placenta and also be transferred to offspring through the milk. Exposing healthy pregnant or breastfeeding subjects who do not have an orthopoxvirus infection to an experimental product.	Yes	Not applicable
Have a history of any clinically significant conditions.	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			dose, not a concern for efficacy.
Have any limitation of activity related to cardiac disease.	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.
Have a bleeding disorder diagnosed by a doctor, or a history of significant bruising or bleeding with intramuscular injections or blood draws.	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product. Study required blood draws and did not want to add complications for subjects.	No	Relevant to clinical trial participants
Currently using certain medications.	Avoiding combination use with certain cytochrome P450 (CYP)3A products, as well as CYP2C8 and CYP2C19 products, as tecovirimat may be a weak inducer or inhibitor.	No	Human clinical drug interaction data demonstrates tecovirimat to be an inducer of CYP3A4 and CYP2B6 and a weak inhibitor of CYP2C8 and CYP2C19. Monitoring is advised during co-administration of tecovirimat with CYP3A4 and CYP2B6 substrates as well as CYP2C8 and CYP2C19 substrates that have narrow therapeutic windows. More information is

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			provided in the SmPC section 4.5.
Have a malignancy that is active or a treated malignancy for which there is no reasonable assurance of sustained cure, or malignancy that is likely to recur during the study.	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.
Have a history of seizure.	Noted seizure activity when tecovirimat administered to dogs at doses of 300 mg/kg/day. Human maximum exposure levels set based on blood exposures in dogs at 100 mg/kg/day that did not produce seizures. Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	Human maximum exposure levels set based on blood exposures in dogs at 100 mg/kg/day that did not produce seizures.
Have a clinically significant blood dyscrasia	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.
Have a history of drug allergy that contraindicates participation in the trial	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	Hypersensitivity to tecovirimat or excipients is contraindicated.

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	No direct drug allergies to tecovirimat have been determined to date. Potential for allergies to drug product excipients.		
Have a medical, psychiatric, or social condition or any occupational reason, or other responsibility that in the judgment of the investigator would render the subject unable to comply with the protocol	Not using subjects who will not be able to fully participate in the study and attend all medical appointments as required	No	Specific to conduct of clinical trial only.
Have an inability to swallow medication	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	Additional labelling instructions for administering the product to those unable to swallow are included in the product information.
Have a clinically significant abnormal ECG.	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	ECG clinical study conducted demonstrating no issue with QTc prolongation with tecovirimat.
Have participated in a clinical trial within 30 days of study entry or planning to participate in any experimental treatment study during the study period	Avoid possible interactions with other experimental drugs that would confound results in a tecovirimat study.	No	Relevant to clinical trial participants only.
Have a history of/ or current drug or alcohol abuse	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	Do not anticipate drug interactions with alcohol and clinical studies in subjects with

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			hepatic impairment did not indicate metabolism issues with tecovirimat.
Have received immunisations/vaccines	Exposing subjects who do not have an orthopoxvirus infection to an experimental product. Potential for interference between tecovirimat and the vaccine.	No	No vaccine-drug interaction studies have been performed in human subjects. Some animal studies have indicated that co-administration of tecovirimat at the same time as live smallpox vaccine (vaccinia virus) may reduce the immune response to the vaccine.
Have a current clinically significant acute bacterial, fungal, or mycobacterial infection requiring administration of systemic antibiotics	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.
Have known chronic bacterial, mycobacterial, fungal, parasitic, or protozoal infection with the exception of clinically significant dermal infections	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Have known hepatitis B or C infection, or positive test result	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.
Have known HIV infection or AIDS or a positive test for HIV	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	Yes	Not applicable
Have a current clinically significant viral infection	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.
Have known clinically significant chronic viral infection	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.
Have received treatment with greater than 20 mg prednisone or equivalent dose or any	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	Yes	Not applicable

Exclusion criteria	Reasons for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
immunosuppressant or immunomodulary medication			
Have abnormal laboratory testing during screening	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy.
Have a greater than or equal than 20% risk of suffering a major cardiovascular event	Exposing sick subjects who do not have an orthopoxvirus infection to an experimental product.	No	The lack of data in patients with active orthopoxvirus infections is not a concern for safety and, based on nonclinical data and the method used to identify the human dose, not a concern for efficacy
Have been previously enrolled in this or any clinical trial involving tecovirimat	Avoid giving healthy subjects who do not have an orthopoxvirus infection multiple exposures to an experimental antiviral product.	No	Relevant to clinical trial participants only

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Because tecovirimat is a novel therapeutic agent, adverse events of the pharmacological class are unknown.

In the pivotal Phase 3 study (SIGA-246-008) tecovirimat was given to 359 subjects who have been followed up for either 28 days or 45 days in case the subject presented unresolved adverse events on the day 28 follow-up visit. This reduces the ability to detect late occurring events or events of long latency.

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) adverse reactions or adverse reactions with a long latency, nor has the product been tested in the disease setting.

In the pivotal Phase 3 study (SIGA-246-008) two 600 mg doses of tecovirimat were given daily for 14 days. In the supportive multiple dose studies either two 600 mg doses or one dose of either 800, 600, 400 or 250 mg were given for periods ranging from 2 to 21 days.

In the supportive single dose studies, the percentage of subjects with at least 1 TEAE was generally lower than in the pivotal or multiple-dose studies and showed no clear dose-related trends across studies. Similarly, treatment-related TEAEs were also less frequent than in the pivotal or multiple-dose studies and did not show clear dose-related trends across studies.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development programme
Breastfeeding women	
Paediatric population	Children and adolescents ≤18 years are not included in the clinical development programme
Elderly	5% of subjects were aged 65-80 years old
Subjects with relevant comorbidities: • Immunocompromised subjects	Immunocompromised subjects are not included in the clinical development programme
Population with relevant different ethnic origin	67% of subjects were white, 28% were black, 2% were Asian, and 3% were of other races
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other: • Patients with the target conditions (smallpox, monkeypox, cowpox and vaccinia complications)	Not included in the clinical development programme

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Tecovirimat is not known to have attributes which make it a candidate for intentional overdose, abuse, or illegal use. Therefore, no potential for misuse for illegal purposes is anticipated.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The following adverse reactions were identified during Phase 3 clinical trials with tecovirimat with a frequency of common or very common: headache, dizziness, nausea, diarrhoea, vomiting, abdominal pain upper, dry mouth. While these adverse reactions may be considered as risks due to frequency and potential detrimental impact on the patient's well-being, the clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated and the potential life-threatening nature of the underlying disease. These risks are therefore not considered important for inclusion in the list of safety concerns.

Psychiatric disorders, skin reactions, arthralgia and osteoarthritis were identified during Phase 3 clinical trials with tecovirimat with a frequency of uncommon. While these adverse reactions may be considered as risks due to potential clinical consequences, the low frequency is considered acceptable in relation to the severity of the indication treated. These risks are therefore not considered important for inclusion in the list of safety concerns.

Resistance - the possibility of resistance to tecovirimat is included in Section 5.1 of the proposed SmPC. As there are no known instances of naturally occurring tecovirimat resistant orthopoxviruses, this risk is not considered important for inclusion in the list of safety concerns.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Headache, dizziness, nausea, diarrhoea, vomiting, abdominal pain upper, dry mouth

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Psychiatric disorders, skin reactions, arthralgia, osteoarthritis

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

None

Known risks that do not impact the risk-benefit profile:

Drug-drug interactions

Other reasons for considering the risks not important:

Resistance – while there is a possibility of tecovirimat resistance, there are no known instances of naturally occurring tecovirimat resistant orthopoxviruses.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks:

There are no important identified risks associated with treatment with tecovirimat.

Important Potential Risks:

There are no important potential risks associated with treatment with tecovirimat.

Missing information 1: Use in pregnancy and lactation

Risk-benefit impact

Pregnant and breastfeeding women were excluded from enrolment in the clinical development programme thus the risks of use in this population cannot be defined. The safety profile for this population will be derived from routine and additional PV activities, if tecovirimat is administered to pregnant and breastfeeding woman in the event of an intentional virus release, a natural outbreak, or complications arising during a mass vaccination campaign.

Missing information 2: Use in immunocompromised subjects

Risk-benefit impact

Immunocompromised subjects were not included in the clinical development programme thus the risks of use in this population cannot be defined. The safety profile for this population will be derived from routine and additional PV activities, if tecovirimat is administered to immunocompromised patients in the event of an intentional virus release, a natural outbreak, or complications arising during a mass vaccination campaign.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable, this is the first RMP submitted for tecovirimat.

SVII.3 Details of important identified risks, important potential risks, and missing information.

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risks:

There are no important identified risks associated with treatment with tecovirimat.

Important Potential Risks:

There are no important potential risks associated with treatment with tecovirimat

SVII.3.2. Presentation of the missing information

Missing information: Use in pregnancy and lactation

Evidence source:

Pregnant and breastfeeding women were excluded from enrolment in the clinical development programme thus the risks of use in this population cannot be defined.

Population in need of further characterisation:

Pregnant and breastfeeding women

Missing information: Use in immunocompromised subjects

Evidence source:

Immunocompromised subjects were not included in the clinical development programme thus the risks of use in this population cannot be defined.

Population in need of further characterisation:

Immunocompromised subjects.

Part II: Module SVIII - Summary of the safety concerns

A summary of the safety concerns identified during the clinical programme is provided in the table below.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and lactation Use in immunocompromised subjects

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

As part of routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, the following targeted follow-up forms will be used to address the safety concerns identified in Module SVIII and to obtain structured information regarding use in these missing information patient groups:

- Use in pregnancy and lactation: pregnancy targeted follow-up form and pregnancy outcome follow-up request letter for both ongoing and completed pregnancies.

- Use in immunocompromised subjects: targeted follow-up form for use in immunocompromised subjects.

To ensure that not only cases with reported adverse events from 'missing information' groups are recorded but also cases with favourable outcomes and thereby allow for analysis of the frequency of adverse reactions in the overall population of the respective 'missing information' group, the MAH proposes to include a communication to prescribers with the packaging to advise on the reporting and forwarding of all exposed individuals from the 'missing information' patient groups.

In addition, the MAH will provide summary case report information for those cases of monkeypox, cowpox or complications due to replication of vaccinia that may occur in the European Union for which tecovirimat is used.

III.2 Additional pharmacovigilance activities

There are challenges in relation to the further characterisation of the missing information: use in pregnancy and lactation and use in immunocompromised subjects. Exposure to the product averages approximately two (2) to three (3) cases per year, and barring an outbreak, is unlikely to significantly change. While there may be increased use of the product due to increased awareness and roll-out in new countries, any growth in the size of the population exposed in the coming years may be insufficient to draw any meaningful conclusions regarding use of the product in the missing information categories.

SIGA has agreements in place to supply tecovirimat to Mpox studies that are enrolling new patients.

The Center for Disease Control and Prevention (CDC) in the United States has been collecting data on hundreds of Mpox patients treated with tecovirimat through their expanded access protocol and have agreed to share this data with SIGA. The objective is to provide stockpiled tecovirimat for treatment of non-variola orthopoxvirus infections (e.g. mpox, vaccinia, or other human virus infection identified as an orthopoxvirus) and secondary treatment of complications from replication-competent vaccinia vaccine in adults and children. To monitor clinical use of tecovirimat under this expanded access IND program, occurrence of serious adverse events and/or selected adverse events of interest, patient treatment, and outcomes information are also intended to be collected to the extent feasible (e.g., baseline clinical conditions, progression/improvement during or post treatment, recovered or not recovered from orthopoxvirus infection).

There is a single-centre Expanded Access Protocol being conducted in the Central African Republic that aims to provide access to tecovirimat (TPOXX) to patients with monkeypox as well as to generate information about its safety and effectiveness that could help inform future use and clinical development, which has agreed to share its data with SIGA.

Data from multiple studies may be combined in a single report, as a meta-analysis, if enough subjects are not enrolled in any single study.

While naturally occurring monkeypox infections are rising in Africa, the present infrastructure in the region is not adequate for conducting clinical studies and with ongoing political instability, it is not safe for patients or staffing personnel. Vaccinia and cowpox infections are rare and sporadic making it unlikely that adequate data could be gathered in a reasonable amount of time to complete a trial.

In this context, SIGA will undertake a Phase 4, observational smallpox field study as an imposed additional pharmacovigilance activity (Category 2) in the Pharmacovigilance Plan (SIGA-246-021: A Phase 4, Observational Field Study to Evaluate the Safety and Clinical Benefit in TPOXX® (Tecovirimat)-Treated Patients Following Exposure to Variola Virus and Clinical Diagnosis of Smallpox Disease). Details of the study (which is a post-marketing commitment in the United States) are provided in the table below. The inherent limitations of dependence on an outbreak to gather data are acknowledged, and it is noted that any data gathered in relation to the missing information categories would likely be limited, particularly in the pregnant/lactating populations. However, based on the disease epidemiology and exposure projections, the field study is considered the best available option for further characterisation of missing information. See Annex 3 for copy of protocol.

SIGA understands that gathering information concerning "Use in pregnancy and lactation" and "Use in immunocompromised subjects" for the other indications - monkeypox, cowpox and the treatment of complications due to replication of vaccinia virus following vaccination against smallpox, will not be captured by the US Field Study. To this regard, it would be difficult to gather this data as part of a field study for the reasons listed above. SIGA commits to submitting summary case report information of any cases involving pregnancy and lactation or immunocompromised patients in the above mentioned indications, and discussing them in context healthy individuals whom have taken Tecovirimat SIGA and other patients who were either pregnant and lactating or immunocompromised.

Study identifier	SIGA-246-021 (A Phase 4, Observational Field Study to Evaluate the Safety and Clinical Benefit in TPOXX® (Tecovirimat)-Treated Patients Following Exposure to Variola Virus and Clinical Diagnosis of Smallpox Disease)
Rationale and study objectives	The purpose of this field study is to evaluate the safety, survival status, time to death, and smallpox rash progression in patients who are receiving tecovirimat for the treatment of smallpox in the United States. This study is being conducted as a Food and Drug Administration (FDA) regulatory post-marketing commitment for the tecovirimat New Drug Application. Primary Objectives: The primary objectives of this study are as follows: • To assess the overall survival at Day 44 (±2 days) following treatment with tecovirimat in patients with smallpox

	• To evaluate the safety and tolerability of tecovirimat treatment in patients with smallpox Secondary Objectives: The secondary objectives of this study are to evaluate the following in patients with smallpox: • Survival status following completion of 14 days of treatment with tecovirimat • Time to death following treatment with tecovirimat, and • Rash progression associated with treatment with tecovirimat Exploratory Objective: The exploratory objective of this study is as follows: • To evaluate plasma concentrations of tecovirimat from any available samples.
Study design	Phase 4, observational field study to evaluate the safety and clinical benefit in tecovirimat-treated patients following exposure to variola virus and clinical diagnosis of smallpox disease.
Study population	Adult and paediatric patients (who weigh ≥13 kg) who receive tecovirimat as part of their medical treatment for variola virus infection in the United States. The study anticipates continuing enrolment for five (5) years or until 100 patients have completed the study (Day 44 ± 2 days), whichever comes first, and will remain open between smallpox outbreaks.
Milestones	Protocol Submission: Submitted to U.S. FDA on 7 JUN 2019. Date of initiation: Formal enrolment was opened on 1 JAN 2020 in the U.S. The study is not yet initiated as no patients have been diagnosed with smallpox. Start of data collection: Not yet initiated. Study does not start enrolling patients until the first case of smallpox is noted. Date for completion: To be provided in annual re-assessment and no later than 12 months after the last administration of tecovirimat for the treatment of smallpox or last data collection in case of retrospective data collection.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.3: On-going and planned additional pharmacovigilance activities.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
SIGA-246-021 (A Phase 4, Observational Field Study to Evaluate the Safety and Clinical Benefit in TPOXX® (Tecovirimat)-Treated Patients Following Exposure to Variola Virus and Clinical Diagnosis of Smallpox Disease) Planned	Observational field study to evaluate safety and clinical benefit in tecovirimat-treated patients following exposure to variola virus and clinical diagnosis of smallpox disease.	Missing information: Use in pregnancy and lactation Use in immunocompromised subjects	Start date Final report	Study will start with enrolling patient when the first case of smallpox is noted To be provided in annual re-assessment and no later than 12 months after the last administration of tecovirimat for the treatment of smallpox or last data collection in case of retrospective data collection.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Tecovirimat, which is currently satisfied by providing timely results from studies: 1. Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children (United States – CDC) 2. Expanded access protocol for the use of tecovirimat for the treatment of monkeypox infection (Central African Republic) Ongoing	To monitor the safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus in the Expanded Access for Treatment of Human Non-Variola Orthopoxvirus and Mpox in the expanded access for the treatment of monkeypox infection.	Missing information: Use in pregnancy and lactation Use in immunocompromised subjects		Annually (with annual re-assessment) and no later than 12 months after the last administration of tecovirimat or last data collection in case of retrospective data collection for each study
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

In terms of gathering further data through clinical trials, there are significant ethical, feasibility and scientific issues that preclude the conduct of controlled clinical trials evaluating antiviral efficacy versus orthopoxviruses. Therefore, evaluation of tecovirimat efficacy within the context of naturally occurring disease remains the only possibility for conducting a controlled clinical trial.

SIGA has agreements in place to supply tecovirimat to Mpox studies that are enrolling new patients.

The MEURI study is an adaptive multiregional international global randomized, placebo-controlled trial that will provide tecovirimat access to patients with mpox during the multi-country outbreak while clinical trials cannot be immediately initiated, maintaining ethics and regulatory oversight; and ensuring data monitoring, reporting and sharing. The primary objective is to evaluate the clinical efficacy, as assessed by time to lesion resolution, of treatment plus SOC versus placebo plus SOC for patients with monkeypox. The secondary objectives are to evaluate the clinical efficacy of treatment plus SOC versus placebo plus SOC in patients with monkeypox as assessed by mortality, clinical severity, and duration of symptoms and the safety of treatment plus SOC relative to placebo plus SOC in patients with monkeypox. Data on the missing information Use in pregnancy and lactation and Use in immunocompromised subjects might also be collected.

The A5418 (STOMP) study is a randomized, placebo-controlled, double-blind study to establish the efficacy of tecovirimat for the treatment of people with laboratory-confirmed or presumptive HMPXV disease. The primary outcome measure will be the time to clinical resolution, defined as the first day on which all skin lesions are scabbed, desquamated or healed, and visible mucosal lesions are healed [Time Frame: Up to day 29]. It is being conducted by the U.S. National Institute of Health (NIH) will most likely be the one completed first. Data on the missing information Use in pregnancy and lactation and Use in immunocompromised subjects might also be collected.

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study **Status**	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new	To evaluate the clinical efficacy and monitor the safety of Tecovirimat in the treatment of the Mpox viral infections in the MEURI and STOMP studies	Long term efficacy and safety Use in pregnancy and lactation Use in immunocompromised subjects	Annually (with annual re-assessment) and no later than 12 months after the last administration of tecovirimat or last data collection in case of retrospective data collection for each study	

information concerning the safety and efficacy of Tecovirimat, which is currently satisfied by providing timely results from studies: 3. MEURI - Emergency use protocol for tecovirimat for monkeypox under MEURI framework (World Health Organization) 4. A5418 / STOMP - Study of Tecovirimat for Human Monkeypox Virus (STOMP) (United States – NIH) Ongoing			

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Use in pregnancy and lactation	Routine risk communication: *SmPC section 4.6* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Legal status: The product will not be available in the typical pharmaceutical commercial stream, but rather will be sold to governments in order to be stockpiled in case of specific need (either singular cases or a specific outbreak of orthopoxvirus). When a case, or cases, occur, the government will send the product specifically to where it is needed for dispensing by medical professionals.*
Use in immunocompromised subjects	Routine risk communication: *SmPC section 4.4* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Legal status: The product will not be available in the typical pharmaceutical commercial stream, but rather will be sold to governments in order to be stockpiled in case of specific need (either singular cases or a specific outbreak of orthopoxvirus). When a case, or cases, occur, the government will send the product specifically to where it is needed for dispensing by medical professionals.*

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnancy and lactation	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* *Legal status* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Targeted follow-up form* *Communication to prescribers to be included with the packaging to advise on the reporting and forwarding of all exposed individuals from the 'missing information' patient groups.* *Summary case report information for any cases involving pregnancy and lactation or immunocompromised patients in the following indications: monkeypox, cowpox and the treatment of complications due to replication of vaccinia virus following vaccination against smallpox* Additional pharmacovigilance activities: *Observational smallpox field study* (SIGA-246-021) *In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Tecovirimat, which is currently satisfied by providing timely results from studies:* *1. Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children (United States – CDC)* *2. Expanded access protocol for the use of tecovirimat for the treatment of*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		monkeypox infection (Central African Republic
Use in immunocompromised subjects	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2* *Legal status* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Targeted follow-up form* *Communication to prescribers to be included with the packaging to advise on the reporting and forwarding of all exposed individuals from the 'missing information' patient groups.* *Summary case report information for any cases involving pregnancy and lactation or immunocompromised patients in the following indications: monkeypox, cowpox and the treatment of complications due to replication of vaccinia virus following vaccination against smallpox* Additional pharmacovigilance activities: *Observational smallpox field study* (SIGA-246-021) *In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Tecovirimat, which is currently satisfied by providing timely results from studies:* *1. Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children (United States – CDC)* *2. Expanded access protocol for the use of tecovirimat for the treatment of monkeypox infection (Central African Republic)*

Part VI: Summary of the risk management plan

Summary of risk management plan for Tecovirimat SIGA (tecovirimat monohydrate)

This is a summary of the risk management plan (RMP) for Tecovirimat SIGA. The RMP details important risks of Tecovirimat SIGA, how these risks can be minimised, and how more information will be obtained about Tecovirimat SIGA's risks and uncertainties (missing information).

Tecovirimat SIGA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tecovirimat SIGA should be used.

This summary of the RMP for Tecovirimat SIGA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tecovirimat-SIGA's RMP.

I. The medicine and what it is used for

Tecovirimat-SIGA is authorised for the treatment of viral infections (cowpox, monkeypox, smallpox) and to treat complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg (see SmPC for the full indication). It contains tecovirimat monohydrate as the active substance and it is given by mouth as hard capsules.

Further information about the evaluation of Tecovirimat SIGA's benefits can be found in Tecovirimat-SIGA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Tecovirimat SIGA, together with measures to minimise such risks and the proposed studies for learning more about Tecovirimat SIGA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Tecovirimat SIGA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Tecovirimat SIGA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tecovirimat SIGA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and lactation Use in immunocompromised patients

II.B Summary of important risks

Missing information No. 1: Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* *Legal status* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	*In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Tecovirimat, which is currently satisfied by providing timely results from studies:* *1. Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children (United States – CDC)* *2. Expanded access protocol for the use of tecovirimat for the treatment of monkeypox infection (Central African Republic)*
Missing information No. 2: Use in immunocompromised patients	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4*

	PL section 2 *Legal status*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: SIGA-246-021, A Phase 4, Observational Field Study to Evaluate the Safety and Clinical Benefit in TPOXX® (Tecovirimat)-Treated Patients Following Exposure to Variola Virus and Clinical Diagnosis of Smallpox Disease. *In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Tecovirimat, which is currently satisfied by providing timely results from studies:* *1. Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children (United States – CDC)* *2. Expanded access protocol for the use of tecovirimat for the treatment of monkeypox infection (Central African Republic)* See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study short name: SIGA-246-021, *A Phase 4, Observational Field Study to Evaluate the Safety and Clinical Benefit in TPOXX® (Tecovirimat)-Treated Patients Following Exposure to Variola Virus and Clinical Diagnosis of Smallpox Disease*

Purpose of the study: Observational field study to further characterise the efficacy and safety of tecovirimat in the treatment of smallpox.

In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Tecovirimat, which is currently satisfied by providing timely results from studies.

1. Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children

Purpose of the study: To provide stockpiled tecovirimat for treatment of non-variola orthopoxvirus infections (e.g., mpox, vaccinia, or other human virus infection identified as an orthopoxvirus) and secondary treatment of complications from replication-competent vaccinia vaccine in adults and

children. Conducted by U.S. CDC.

2. Expanded access protocol for the use of tecovirimat for the treatment of monkeypox infection Purpose of the study: To provide access to tecovirimat to patients with monkeypox as well as to generate information about its safety and effectiveness that could help inform future use and clinical development.

3. MEURI - Emergency use protocol for tecovirimat for monkeypox under MEURI framework

Purpose of the study: To provide access to tecovirimat to patients with mpox during the multi-country outbreak while clinical trials cannot be immediately initiated, maintaining ethics and regulatory oversight; and ensuring data monitoring, reporting and sharing. Data on the missing information Use in pregnancy and lactation and Use in immunocompromised subjects might also be collected.

4. A5418 / STOMP - Study of Tecovirimat for Human Monkeypox Virus (STOMP)

Purpose of the study: To establish the efficacy of tecovirimat for the treatment of people with laboratory-confirmed or presumptive HMPXV disease. Data on the missing information Use in pregnancy and lactation and Use in immunocompromised subjects might also be collected.

II.C.2 Other studies in post-authorisation development plan

There are no other studies in post-authorisation development plan.

Part VII: Annexes

Annex 1 – EudraVigilance Interface
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan
Annex 4 – Specific adverse drug reaction follow-up forms
Annex 5 - Protocols for proposed and on-going studies in RMP part IV
Annex 6 - Details of proposed additional risk minimisation activities (if applicable)
Annex 7 - Other supporting data (including referenced material)
Annex 8 – Summary of changes to the risk management plan over time

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

Study	**Summary of objectives**	**Safety concerns addressed**	**Protocol link Milestones**
SIGA-246-021 (A Phase 4, Observational Field Study to Evaluate the Safety and Clinical Benefit in TPOXX® (Tecovirimat)-Treated Patients Following Exposure to Variola Virus and Clinical Diagnosis of Smallpox Disease) Category 2	Observational field study to evaluate safety and clinical benefit in tecovirimat-treated patients following exposure to variola virus and clinical diagnosis of smallpox disease.	Missing information: Use in pregnancy and lactation Use in immunocompromised subjects	Annex 3 Final report: To be provided in annual re-assessment and no later than 12 months after the last administration of tecovirimat for the treatment of smallpox or last data collection in case of retrospective data collection".

In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Tecovirimat, which is currently satisfied by providing timely results from studiesIn order to ensure adequate monitoring of safety of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children, the MAH shall provide yearly updates on any new information concerning the safety of Tecovirimat, which is currently satisfied by providing timely results from studies: 1. Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus	To monitor the safety and efficacy of Tecovirimat in the treatment of the Smallpox, Mpox, Cowpox viral infections and complications due to replication of vaccinia virus in the Expanded Access for Treatment of Human Non-Variola Orthopoxvirus and Mpox in the expanded access for the treatment of monkeypox infection.	Missing information: • Use in pregnancy and lactation • Use in immunocompromised subjects	Annually (with annual re-assessment) and no later than 12 months after the last administration of tecovirimat or last data collection in case of retrospective data collection for each study

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
Infections in Adults and Children (United States – CDC) 2. Expanded access protocol for the use of tecovirimat for the treatment of monkeypox infection (Central African Republic)			

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

- SIGA-246-021 protocol Version 1.0 dated 24 May
- CDC Expanded Access
- CAR Expanded Access

As SIGA is not the sponsor of the mpox trials and remains under confidentiality with individual sponsors, we cannot disclose trial protocols. The links to the protocols are as follows:

- https://www.cdc.gov/poxvirus/monkeypox/clinicians/obtaining-tecovirimat.html#Tecovirimat-IND-Protocol

- https://www.isrctn.com/ISRCTN43307947

The CDC Expanded Access protocol is publicly available (attached).

Annex 4 - Specific adverse drug reaction follow-up forms

- Use in pregnancy and lactation
- Use in immunocompromised subjects

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

- Emergency use protocol for tecovirimat for monkeypox under MEURI framework (World Health Organization)
- STOMP (stomptpoxx.org)

As SIGA is not the sponsor of the mpox trials and remains under confidentiality with individual sponsors, we cannot disclose trial protocols. The links to the protocols are as follows:

- https://www.who.int/publications/m/item/core-protocol---an-international-adaptive-multi-country-randomized-placebo-controlled--double-blinded-trial-of-the-safety-and-efficacy-of-treatments-for-patients-with-monkeypox-virus-disease
- https://clinicaltrials.gov/ct2/show/NCT05534984?cond=monkeypox&draw=2&rank=8

The MEURI Expanded Access trial protocol is publicly available (attached).

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable – no additional risk minimisation activities are proposed.

Annex 7 - Other supporting data (including referenced material)

A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease. Available at: https://clinicaltrials.gov/ct2/show/NCT05534984?cond=monkeypox&draw=2&rank=8

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CDC Information for Healthcare Providers: Tecovirimat (TPOXX) for Treatment of Mpox. Available at: https://www.cdc.gov/poxvirus/monkeypox/clinicians/obtaining-tecovirimat.html#Tecovirimat-IND-Protocol

CORE PROTOCOL - An international adaptive multi-country randomized,placebo-controlled, double-blinded trial of the safety and efficacy of treatments for patients with monkeypox virus disease. Available at: https://www.who.int/publications/m/item/core-protocol---an-international-adaptive-multi-country-randomized-placebo-controlled--double-blinded-trial-of-the-safety-and-efficacy-of-treatments-for-patients-with-monkeypox-virus-disease

Clinical management and infection prevention and control guideline. Available at: https://www.who.int/teams/health-care-readiness/clinical-management-of-monkeypox#:~:text=Emergency%20use%20protocol%20for%20tecovirimat%20for%20monkeypox%20under,%20Weight-based%20dosing.%20%207%20more%20rows%20

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Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
1.0	06 January 2022 EMEA/H/C/005248/IB/0001	Initial version
1.1	20 July 2022 EMEA/H/C/005248/IB/0001	The title page has been updated to include details of the currently approved RMP. The RMP Part III.1 and Annex 4 has been updated to remove reference to submission of targeted follow-up forms for pregnancy and immunocompromised subjects within 2 months after MA approval since the forms were provided in the previous RMP update. Additionally, in RMP Part III.1, reference to submission of communication to prescribers within 2 months after MA approval has also been removed. A communication has been prepared and submitted with this RMP update as requested. Annex 8 has been updated to include a list of all significant changes to the RMP over time.