ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tecovirimat SIGA 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains tecovirimat monohydrate equivalent to 200 mg tecovirimat.

Excipient(s) with known effect

Each capsule contains 31.5 mg lactose (as monohydrate) and 0.41 mg sunset yellow (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

Opaque gelatin capsules with an orange body and black cap, containing white to off-white powder. The body is printed with "SIGA" and the SIGA logo (a curved triangle with letters in it) followed by "®" in white ink. The cap is printed with "ST-246®" in white ink. The capsules are 21.7 millimeters long and 7.64 millimeters in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Smallpox
- Cowpox

Tecovirimat SIGA 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 (see sections 4.4 and 5.1).

Tecovirimat SIGA should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Tecovirimat treatment should be initiated as soon as possible after diagnosis (see section 4.1).

Adults and children of at least 13 kg
The recommended doses are described in Table 1.

Table 1: Recommended dose by body weight

Body Weight	Dosage	Number of Capsules
13 kg to less than 25 kg	200 mg every 12 hours for 14 days	One Tecovirimat 200 mg capsule
25 kg to less than 40 kg	400 mg every 12 hours for 14 days	Two Tecovirimat 200 mg capsules
40 kg to less than 120 kg	600 mg every 12 hours for 14 days	Three Tecovirimat 200 mg capsules
120 kg and above	600 mg every 8 hours for 14 days	Three Tecovirimat 200 mg capsules

Re-dosing in case of vomiting
If vomiting occurs within 30 minutes of taking tecovirimat hard capsules, another dose may be administered immediately. If vomiting occurs more than 30 minutes after taking tecovirimat hard capsules, no additional dose should be given and dosing should resume as usual after 12 hours.

Special populations

Elderly
No dosage adjustment is required (see section 5.2).

Renal impairment
No dosage adjustment is required (see section 5.2).

Hepatic impairment
No dosage adjustment is required (see section 5.2).

Paediatric population
Tecovirimat should not be administered to children of less than 13 kg body weight.
No dose recommendations for children less than 13 kg body weight have been established.

Method of administration

Oral use.
Tecovirimat hard capsules should be taken within 30 minutes after a meal of moderate or high fat (see section 5.2).

For patients who cannot swallow tecovirimat hard capsules, the capsules may be opened and the contents may be mixed with approximately 30 mL of liquid (e.g. milk) or soft food (e.g. yogurt) and swallowed within 30 minutes of completing a meal (see sections 5.2 and 6.3).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Co-administration of other medicinal products

Co-administration of repaglinide and tecovirimat may cause mild to moderate hypoglycaemia, (see section 4.5). Blood glucose and hypoglycaemic symptoms should be monitored when administering tecovirimat with repaglinide.

Co-administration of midazolam and tecovirimat may reduce the effectiveness of midazolam (see section 4.5). Effectiveness of midazolam should be monitored when administering tecovirimat with midazolam.

Renal impairment

Tecovirimat should be used with caution in patients with severe renal impairment as there is limited clinical data in this population and higher unbound drug and metabolites levels may be observed. (see sections 4.2 and 5.2).

Hepatic impairment

Tecovirimat should be used with caution in patients with severe hepatic impairment as there is limited clinical data in this population and higher unbound drug and metabolite levels may be observed (see sections 4.2 and 5.2).

Immunocompromised population

The safety and efficacy of tecovirimat has not been evaluated in immunocompromised individuals. Nonclinical studies using animal models indicate that tecovirimat may have reduced efficacy in immunocompromised individuals. (See section 5.1).

Excipients

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains sunset yellow (E110). May cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on tecovirimat

Tecovirimat is a substrate of UGT1A1, 1A3 and 1A4. Co-administration of tecovirimat with strong inhibitors or inducers of these UGTs is not expected to have a clinically important effect on tecovirimat exposures.

Tecovirimat was studied in people against phosphate binders with the results indicating a slight increase in exposure of tecovirimat. See Table 2 for results.

Table 2: Interactions and dose recommendations with tecovirimat

Medicinal Product by therapeutic area[a]	**Effect on tecovirimat levels. Mean percent change in AUC, C_{max}**	**Recommendation concerning co-administration with Tecovirimat**
Phosphate Binders[a]:		
Calcium acetate	Tecovirimat: AUC: ↑ 16% C_{max}: ↑ 9%	A risk for increase in tecovirimat plasma concentrations cannot be excluded when co-administered with phosphate binders. Monitor for signs or symptoms of adverse effects when Tecovirimat SIGA is co-administered with phosphate binders.
Lanthanum carbonate	Tecovirimat: AUC: ↑ 23% C_{max}: ↑ 21%	
Sevelamer carbonate	Tecovirimat: AUC: ↑ 27% C_{max}: ↑ 16%	

Sucroferric oxyhydroxide	Tecovirimat: AUC: ↑ 21% C_{max}: ↑ 15%	

[a]These interactions have been studied in healthy adults.

Effect of tecovirimat on other medicinal products

Tecovirimat and its M4 metabolite are inducers of cytochrome P450 (CYP)3A and CYP2B6. Co-administration with tecovirimat may lead to reduced plasma exposures of sensitive substrates of CYP3A4 or CYP2B6, potentially leading to reduced effects. Monitoring is advised during co-administration of tecovirimat with CYP3A4 and CYP2B6 substrates that have narrow therapeutic windows. See Table 3 for some examples.

Tecovirimat is a weak inhibitor of CYP2C8 and CYP2C19. Co-administration with tecovirimat may lead to increased plasma exposures of sensitive substrates of CYP2C8 or CYP2C19, potentially leading to increased adverse effects. Monitoring is advised during co-administration of tecovirimat with CYP2C8 and CYP2C19 substrates that have narrow therapeutic windows. See Table 3 for some examples.

Table 3: Interactions and dose recommendations with other medicinal products

Medicinal Product by therapeutic area[a]	**Effect on medicinal product levels. Mean percent change in AUC, C_{max}**	**Recommendation concerning co-administration with Tecovirimat**
Antidepressant:		
Bupropion[a] (150 mg)	Decreased Bupropion AUC: ↓ 15% C_{max}: ↓ 14%	No dose adjustment is required. The effectiveness of bupropion should be monitored.
Antidiabetics:		
Repaglinide[a] (2 mg)	Repaglinide: AUC: ↑ 27% C_{max}: ↑ 27%	Tecovirimat is a weak inhibitor of CYP2C8 and caused an increase in repaglinide plasma concentrations. Co-administration of repaglinide and tecovirimat may cause mild to moderate hypoglycemia. Blood glucose and hypoglycemic symptoms should be monitored in patients when tecovirimat is co-administered with repaglinide.
Antifungals		
Voriconazole	Interactions not studied Expected AUC: ↑ C_{max}: ↑	A risk for increase in voriconazole plasma concentrations cannot be excluded (CYP2C19 substrate). The combination of tecovirimat and voriconazole should be used with caution.
Antiviral - non-nucleoside reverse transcriptase inhibitor		
Rilpivirine	Interactions not studied Expected AUC: ↓ C_{max}: ↓	A risk for decreases in rilpivirine plasma concentrations cannot be excluded (CYP3A4 substrate). The combination of tecovirimat and rilpivirine should be used with caution.
CCR5 antagonists		

Maraviroc	Interactions not studied Expected AUC: ↓ C_{max}: ↓	A risk for decreases in maraviroc plasma concentrations cannot be excluded (CYP3A4 substrate). The combination of tecovirimat and maraviroc should be used with caution.
CNS Depressant:		
Midazolam[a] (2 mg)	Midazolam: AUC: ↓ 32% C_{max}: ↓ 39%	Tecovirimat is a weak inducer of CYP3A4 and caused a decrease in plasma concentrations of midazolam. The effectiveness of midazolam should be monitored and the dose adjusted as necessary.
HMG CO-A Reductase Inhibitors		
Atorvastatin	Interactions not studied Expected AUC: ↓ C_{max}: ↓	A risk for decreases in atorvastatin plasma concentrations cannot be excluded (CYP3A4 substrate). The combination of tecovirimat and atorvastatin should be used with caution.
Immunosuppressants		
Tacrolimus	Interactions not studied Expected AUC: ↓ C_{max}: ↓	A risk for decreases in tacrolimus plasma concentrations cannot be excluded (CYP3A4 substrate). The combination of tecovirimat and tacrolimus should be used with caution.
Narcotic Analgesics		
Methadone	Interactions not studied Expected AUC: ↓ C_{max}: ↓	A risk for decreases in methadone plasma concentrations cannot be excluded (CYP2B6 substrate). The combination of tecovirimat and methadone should be used with caution.
Nonsteoidal anti-inflammatory		
Flurbiprofen[a] (50 mg)	Flurbiprofen: AUC: ↔ C_{max}: ↔	No dose adjustment is required.
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil Tadalafil Vardenafil	Interactions not studied Expected AUC: ↓ C_{max}: ↓	A risk for decreases in PDE-5 inhibitor plasma concentrations cannot be excluded (CYP3A4 substrate). The combination of tecovirimat and PDE-5 inhibitors should be used with caution.
Protease inhibitors (PIs)		
Darunavir	Interactions not studied Expected AUC: ↓ C_{max}: ↓	A risk for decreases in darunavir plasma concentrations cannot be excluded (CYP3A4 substrate). The combination of tecovirimat and darunavir should be used with caution.

Proton Pump Inhibitors:		
Omeprazole[a] (20 mg)	Omeprazole AUC: ↑ 73% C_{max}: ↑ 83%	Tecovirimat is a weak inhibitor of CYP2C19 and caused an increase in plasma concentrations of omeprazole. The combination of tecovirimat and proton pump inhibitors should be used with caution.
Lansoprazole Rabeprazole	Interactions not studied Expected AUC: ↑ C_{max}: ↑	

[a]These interactions have been studied in healthy adults to evaluate the effect of repeated doses of tecovirimat 600 mg twice daily on the single-dose PK of probe substrates.

Vaccine

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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no data from the use of tecovirimat in pregnant women.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
Tecovirimat is not recommended during pregnancy.

Breast-feeding

It is unknown whether tecovirimat/metabolites are excreted in human milk.
Available toxicological/safety data in animals have shown excretion of tecovirimat in milk (see section 5.3).
A risk to the newborns/infants cannot be excluded.
Breast-feeding should be discontinued during treatment with tecovirimat.

Fertility

The effects of tecovirimat on fertility in humans have not been studied.
Tecovirimat caused decreased fertility due to testicular toxicity in male mice (see section 5.3).

4.7 Effects on ability to Drive and use Machines

Tecovirimat has minor influence on the ability to drive and use machines. Patients should be informed about the possible occurrence of dizziness and should be cautioned about driving or operating machines until they know how tecovirimat will affect them.

4.8 Undesirable Effects

Summary of the safety profile

The most frequently reported adverse drug reactions were headache (12.3%) and nausea (4.5%).

Tabulated summary of adverse reactions

Adverse reactions are classified according to System Organ Class and frequency. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 4: Frequency of Adverse Reactions by System Organ Class from Clinical Trials

System organ class	Very common	Common	Uncommon
Blood and lyphatic system disorders			Haematocrit Decreased Haemoglobin Decreased Leucopoenia Thrombocytopenia
Metabolism and nutrician disorders			Decreased appetite
Hepatobiliary disorders			Elevated LFT
Psychiatric disorders			Anxiety Depression Dysphoria Irritability Panic attack
Nervous system disorders	Headache	Dizziness	Disturbance in attention Dysgeusia Electroencephalogram abnormal Insomnia Migraine Somnolence Paraesthesia
Cardiac disorders			Heart Rate Increased Palpitations
Respiratory, thoracic and mediastinal disorders			Oropharyngeal pain
Gastrointestinal disorders		Abdominal pain upper Abdominal discomfort Diarrhoea Nausea Vomiting	Abdominal distention Aphthous ulcer Chapped lips Constipation Dry mouth Dyspepsia Eructation Flatulence Gastrooesophageal reflux disease Infrequent bowel movements Paraesthesia oral
Skin and subcutaneous tissue disorders			Palpable purpura Pruritus generalised Rash Rash pruritic
Musculoskeletal and connective tissue disorders			Arthralgia Osteoarthritis
General disorders and administration site conditions			Chills Fatigue Feeling jittery Malaise Pain Pyrexia Thirst

Paediatric population

Tecovirimat has not been studied in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of overdose, patients should be monitored for any signs or symptoms of adverse reactions. Haemodialysis will not significantly remove tecovirimat in overdosed patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antiviral for systemic use, other antivirals, ATC code: J05AX24.

Mechanism of action

Tecovirimat inhibits the activity of the orthopoxvirus VP37 protein, which is encoded by a highly conserved gene in all members of the orthopoxvirus genus. Tecovirimat blocks the interaction of VP37 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.

Activity in cell culture

In cell culture assays, the effective concentrations of tecovirimat resulting in a 50% reduction in virus induced cytopathic effect (EC_{50}), were 0.016-0.067 µM, 0.015 µM and 0.009 µM, for smallpox, rabbitpox and vaccinia viruses, respectively.

Resistance

Current virologic assessment of mpox shows evidence of resistance, with resistance documented in <1% of isolates. Tecovirimat has a relatively low resistance barrier, and certain amino acid substitutions in the target VP37 protein can confer large reductions in tecovirimat antiviral activity. Resistance mutations have arisen in patients receiving prolonged tecovirimat treatment for mpox, particularly in immunocompromised patients, such as HIV patients with low CD4 T-cell counts. The possibility of resistance to tecovirimat should be considered in patients either who fail to respond to therapy or who develop recrudescence of disease after an initial period of responsiveness.

Clinical efficacy

There is no human efficacy data available for the treatment of smallpox, cowpox or complications due to replication of vaccinia virus following vaccination against smallpox.

Nonclinical efficacy

Efficacy studies were conducted in cynomolgus macaques infected with mpox virus, using a lethal model broadly accepted as a model for human smallpox, and New Zealand White (NZW) rabbits infected with rabbitpox virus. The primary efficacy endpoint for these studies was survival. In non-human primate studies, cynomolgus macaques were lethally challenged intravenously with 5×10^7 plaque-forming units of mpox virus. Tecovirimat was administered orally once daily at a dose level of 10 mg/kg for 14 days, starting at Day 4, 5 or 6 post-challenge. In rabbit studies, NZW rabbits were lethally challenged intradermally with 1,000 plaque-forming units of rabbitpox virus. Tecovirimat was administered orally once daily for 14 days at a dose level of 40 mg/kg, starting at Day 4 post-

challenge. The timing of tecovirimat dosing in these studies was intended to assess efficacy when treatment is initiated after animals have developed clinical signs of disease, specifically dermal pox lesions in cynomolgus macaques and fever in rabbits. Clinical signs of disease were evident in some animals at Day 2-3 post-challenge but were evident in all animals by Day 4 post-challenge. Survival was monitored for 3-6 times the mean time to death for untreated animals in each model.

Treatment with tecovirimat for 14 days resulted in statistically significant improvement in survival relative to placebo, except when given to cynomolgus macaques starting at Day 6 post-challenge (Table 5).

Table 5: Survival Rates in Tecovirimat Treatment Studies in Cynomolgus Macaques and NZW Rabbits Exhibiting Clinical Signs of Orthopoxvirus Disease

	Treatment Initiation[a]	**Survival Percentage (No. survived/n)**		**p-value[b]**	**Survival Rate Difference[c] (95% CI)[d]**
		Placebo	**Tecovirimat**		
Cynomolgus Macaques					
Study 1	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8%, 99.5%)
Study 2	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1%, 100%)
Study 3	Day 4	0% (0/3)	83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 5		83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 6		50% (3/6)	0.1231	50% (-28.3%, 90.2%)
NZW Rabbits					
Study 4	Day 4	0% (0/10)	90% (9/10)	< 0.0001	90% (50.3%, 99.8%)
Study 5	Day 4	NA[e]	88% (7/8)	NA	NA

[a]Day post-challenge tecovirimat treatment was initiated.

[b]p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma = 0.000001) compared to placebo.

[c]Survival percentage in tecovirimat treated animals minus survival percentage in placebo treated animals.

[d]Exact 95% confidence interval based on the score statistic of difference in survival rates.

[e]A placebo control group was not included in this study.

KEY: NA = Not Applicable

Pharmacokinetic/pharmacodynamic relationship

The non-human primate (NHP) and rabbit PK/PD models were developed in order to establish the exposure-response relationship between tecovirimat treatment and survival. The dose and regimen for humans were subsequently selected to provide exposures that exceed those associated with the fully effective dose in animals. Analysis of PK/PD models indicates that C_{min} and AUC are the most predictive PK parameters for drug efficacy.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with tecovirimat in one or more subsets of the paediatric population in the treatment of orthopoxvirus disease (smallpox, cowpox and vaccinia) (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under 'exceptional circumstances'. This means that for ethical reasons it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic Properties

Absorption

Tecovirimat reaches maximum plasma concentrations 4 to 6 hours after oral administration with food.

The administration of tecovirimat with a meal of moderate fat and calories (~ 600 calories and ~ 25 grams of fat), as compared to tecovirimat taken in the fasted (unfed) state, increased the drug exposure (AUC) by 39%.

Distribution

Tecovirimat is 77.3-82.2% bound to human plasma proteins. After a single 600 mg dose of [^{14}C]-tecovirimat in healthy subjects, concentrations of total radioactivity were lower in whole blood compared to plasma at all time points, with ratios of whole blood to plasma ranging from 0.62-0.90 across all time points. Tecovirimat has a high volume of distribution (1356 L).

Biotransformation

Based on human studies, tecovirimat is metabolized to form metabolites M4 (N-{3,5-dioxo-4-azatetracyclo[5.3.2.0{2,6}.0{8,10}]dodec-11-en-4-yl}amine), M5 (3,5-dioxo-4-aminotetracyclo[5.3.2.0{2,6}.0{8,10}]dodec-11-ene), and TFMBA (4 (trifluoromethyl) benzoic acid). None of the metabolites is pharmacologically active.

Tecovirimat is a substrate of UGT1A1 and UGT1A4. In urine, primary tecovirimat glucuronide conjugate and M4 glucuronide conjugate were the most abundant components accounting for means of 24.4% and 30.3% of dose, respectively. However, none of the glucuronide conjugates was found as a major metabolite in plasma.

Elimination

After a single dose of [^{14}C]-tecovirimat in healthy subjects, approximately 95% of the [^{14}C]-radioactivity was recovered in urine and faeces over the 192-hour post-dose period, with approximately 73% of the [^{14}C]-radioactivity administered being recovered in urine and 23% being recovered in faeces, indicating that the renal pathway is the major route of excretion. The renal excretion of parent compound was minimal, accounting for less than 0.02%. The majority of drug excreted by the renal system is in a glucuronidated form. In faeces, the excretion was mainly of unchanged tecovirimat. The terminal half-life of tecovirimat was 19.3 hr.

Linearity/non-linearity

Tecovirimat exhibits linear pharmacokinetics over a dose range of 100-600 mg.

Special populations

No clinically significant differences in the pharmacokinetics of tecovirimat were observed in healthy subjects based on age, gender or race.

Renal impairment
In subjects with renal impairment (based on estimated GFR), no clinically significant differences in the pharmacokinetics of tecovirimat were observed.

Hepatic impairment
In subjects with with mild, moderate or severe hepatic impairment (based on Child Pugh Scores A, B or C), no clinically significant differences in the pharmacokinetics of tecovirimat were observed. However, it is possible that patients with severe hepatic impairment may have higher unbound drug and metabolite levels (see sections 4.2 and 5.2).

Paediatric patients
The pharmacokinetics of tecovirimat has not been evaluated in paediatric patients. The recommended paediatric dosing regimen for subjects at least 13 kg body weight is expected to produce tecovirimat exposures that are comparable to those in adult subjects aged 18 to 50 years based on a population pharmacokinetic modeling and a simulation approach.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered in excess of the maximum human exposure indicating little relevance to clinical use.

The non-clinical safety was evaluated in 28-day and 3-month studies in mice and monkeys, respectively. C_{max} exposures at the no observed adverse effect level in the toxicology studies compared to the human C_{max} at the recommended human dose (RHD) have safety margins of 23 based on the mouse and 2.5 based on the monkey. The dog is a more sensitive species to tecovirimat and was tested after a single dose or repeated doses. Six hours after a single dose of 300 mg/kg, one dog experienced convulsions (tonic and clonic) with electroencephalography (EEG) consistent with seizure activity. This dose produce a C_{max} in the dog that was approximately 4 times higher than the highest human C_{max} at the RHD. In the dog, the no observe adverse effect level was determined to be 30 mg/kg with a C_{max} safety margin at the RHD of 1.

Carcinogenicity studies have not been conducted with tecovirimat.

Tecovirimat was not genotoxic in *in vitro* or *in vivo* assays.

In a fertility and early embryonic development study in mice, no effects of tecovirimat on female fertility were observed at tecovirimat exposures (AUC) approximately 24 times higher than human exposure at the RHD. In a fertility and early embryonic development study in mice, no biologically meaningful effects of tecovirimat on male or female fertility were observed at tecovirimat exposures (AUC) approximately 24 times higher than human exposure at the RHD.

Reproductive toxicity studies have been performed in mice and rabbits. Based on pilot studies, the highest dose selected for the definitive study in rabbit was 100 mg/kg and in mice was 1,000 mg/kg. No embryo-foetal toxicities were observed in rabbit at doses up to 100 mg/kg/day (0.4 times the human exposure at the RHD) and no embryo-foetal toxicities were observed at doses up to 1,000 mg/kg/day in mice (approximately 23 times higher than human exposure at the RHD).

No embryo-foetal toxicities were observed at doses up to 100 mg/kg/day in rabbits (0.4 times the human exposure at the RHD). Maternal toxicity was detected in rabbits at 100 mg/kg/day, which included decreases in body weight and mortality.

Available toxicological/safety data in animals have shown excretion of tecovirimat in milk.
In a lactation study at doses up to 1,000 mg/kg/day, mean tecovirimat milk to plasma ratios up to approximately 0.8 were observed at 6 and 24 hours post-dose when administered orally to mice on lactation Day 10 or 11.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule content

Silica, colloidal anhydrous
Croscarmellose sodium (E468)
Hypromellose (E464)
Lactose monohydrate
Magnesium stearate
Cellulose, microcrystalline (E460)
Sodium laurilsulfate (E487)

Capsule shell

Gelatin
Brilliant blue FCF (E133)
Erythrosine (E127)
Sunset yellow (E110)
Titanium dioxide (E171)

Printing ink

Shellac (E904)
Titanium dioxide (E171)
Isopropyl alcohol
Ammonium hydroxide (E527)
Butyl alcohol
Propylene glycol
Simeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

Capsules that have been opened and mixed with food or liquids, should be consumed within 30 minutes (see section 6.6).

6.4 Special precautions for storage

Store below 25°C.
Store in the original package in order to protect from light.
For storage conditions after mixing the medicinal product, see section 6.3.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with a polypropylene child-resistant cap.
Pack-size of 84 (2 bottles of 42) hard capsules.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SIGA Technologies Netherlands B.V.
Prinsenhil 29,
Breda 4825 AX,
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1600/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 JAN 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Millmount Healthcare Limited
Block-7, City North Business Campus,
Stamullen
Co. Meath
K32 YD60
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
SOB 1: In order to further characterise the efficacy and safety of tecovirimat in the treatment of smallpox, the MAH should submit the results of the following open-label controlled phase 4 trial, upon the occurrence of a smallpox outbreak (as per protocol): A Multicenter, Open-Label, Randomized, Controlled Phase 4 Trial to Evaluate the Efficacy and Safety of Brincidofovir, Tecovirimat, and Brincidofovir Plus Tecovirimat for the treatment of Smallpox in Adult and Paediatric Participants.	Annually (with annual re-assessment) and no later than 12 months after the last administration of tecovirimat for the treatment of smallpox
SOB 2: In order to ensure adequate monitoring of safety and efficacy of Tecovirimat in the treatment of the Smallpox, 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.	Annually (with annual reassessment)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tecovirimat SIGA 200 mg hard capsules
tecovirimat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg tecovirimat (as monohydrate)

3. LIST OF EXCIPIENTS

Contains lactose and sunset yellow (E110). See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

84 (2 bottles of 42) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SIGA Technologies Netherlands B.V.
Prinsenhil 29,
Breda 4825 AX,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1600/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tecovirimat

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Tecovirimat SIGA 200 mg capsules
tecovirimat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg tecovirimat (as monohydrate)

3. LIST OF EXCIPIENTS

Contains lactose and sunset yellow (E110). See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

42 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SIGA Technologies Netherlands B.V.
Prinsenhil 29,
Breda 4825 AX,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1600/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Tecovirimat SIGA 200 mg hard capsules
tecovirimat

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecovirimat SIGA is and what it is used for

Tecovirimat SIGA contains the active ingredient tecovirimat.

Tecovirimat SIGA is used to treat viral infections, such as smallpox and cowpox in adults and children weighing at least 13 kg.

Tecovirimat SIGA is also used to treat complications from smallpox vaccines.

Tecovirimat SIGA works by stopping the virus from spreading. This will help your own body to build up protection against the virus until you are better.

2. What you need to know before you take Tecovirimat SIGA

Do not take Tecovirimat SIGA

- if you are allergic to Tecovirimat SIGA or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Tecovirimat SIGA.
- if your immune system does not work properly (immunodeficiency) or you are taking medicines that weaken the immune system (such as high-dose corticosteroids, immunosuppresants or cancer medicines).
- If you have reduced function of your liver or kidneys.

Children weighing less than 13 kg

This medicine should not be given to children who weigh less than 13 kg.

Other medicines and Tecovirimat SIGA

Tell your doctor if you are taking, have recently taken or might take any other medicines.
You must tell your doctor if you are taking any of the following medicines:

- repaglinide (a medicine used to treat blood sugar levels in diabetes)
- omeprazole, lansoprazole, or rabeprazole (used to treat ulcers or heart burn)
- midazolam (a medicine used to put people to sleep before a surgical procedure)
- bupropion (a medicine used to treat depression)
- atorvastatin (a medicine use to treat high cholesterol)
- flurbiprofen (a medicine used to treat pain)
- calcium acetate, lanthanum carbonate, sevelamer carbonate, or sucroferric oxyhydroxide (used to reduce high blood phosphate levels)
- methadone (a medicine used to treat pain or withdrawal symtoms of narcotics)
- darunavir, maraviroc, or rilpivirine (used to treat HIV infection)
- sildenafil, tadalafil, or vardenafil (used to treat erectile dysfunction)
- voriconazole (a medicine used to treat fungus infections)
- tacrolimus (a medicine used to suppress the immune system

Taking Tecovirimat SIGA with any of these may stop your medicines from working properly, or make any side effects worse. Your doctor may need to give you a different medicine or adjust the dose of medicine you are taking. The above is not a complete list of medicines that your doctor may need to alter.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Tecovirimat SIGA is not recommended during pregnancy.

It is not known whether Tecovirmat SIGA is excreted in human milk. Breast-feeding is not recommended during treatment with this medicine. Tell your doctor if you are breast-feeding or are planning to breast-feed before taking this medicine.

Driving and using machines

Do not drive or operate machines if you feel dizzy.

Tecovirimat SIGA contains Lactose and sunset yellow (E110)

- Tecovirimat SIGA contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- This medicine also contains sunset yellow (E110), a colouring agent. This may cause allergic reactions.

3. How to take Tecovirimat SIGA

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

<u>Adults and children weighing at least 13 kg</u>

The recommended doses are described in the table below.

Body Weight	**Dose**
13 kg to less than 25 kg	One Tecovirimat SIGA 200 mg capsule every 12 hours for 14 days (200 mg two times a day)
25 kg to less than 40 kg	Two Tecovirimat SIGA 200 mg capsules every 12 hours for 14 days (400 mg two times a day)
40 kg to less than 120 kg	Three Tecovirimat SIGA 200 mg capsules every 12 hours for 14 days (600 mg two times a day)
120 kg and above	Three Tecovirimat SIGA 200 mg capsules every 8 hours for 14 days (600 mg three times a day)

Method of administration

Take Tecovirimat SIGA within 30 minutes after eating a full meal of at least 600 calories. The meal should contain at least 25 grams of fat. This can be achieved with many common foods (e.g., 2 big handfuls of nuts, 2 tablespoons of oil, or 1.5 tablespoons of butter). This is very important to ensure that a sufficient amount of the medicine is taken up by your body. Swallow the capsules whole with 150ml to 200ml of water.

Adults and children who have difficulty swallowing capsules

For patients who are not able to swallow the capsules, the doctor may recommend opening the hard capsule and mixing the contents with 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt).

Wash and dry your hands before and after preparation. Carefully open the capsule so that the contents do not spill or escape into the air. Hold the capsule with the cap facing up and pull the cap away from the body of the capsule. Use a small container for mixing. Mix the entire contents of the capsule with 30 mL of liquid (e.g. milk) or soft food (e.g. yogurt). The mixture should be taken within 30 minutes after mixing and within 30 minutes of eating a meal.

The recommended paediatric and adult dosage and preparation instructions are given in the table below.

Body weight	**Tecovirimat dose**	**Amount of liquid or soft food**	**Number of capsules**	**Food and tecovirimat mixture instructions**
13 kg to less than 25 kg	200 mg	2 tablespoons	1 Tecovirimat capsule	Mix entire contents of 1 Tecovirimat capsule with 2 tablespoons of liquid or soft food.
25 kg to less than 40 kg	400 mg	2 tablespoons	2 Tecovirimat capsules	Mix entire contents of 2 Tecovirimat capsules with 2 tablespoons of liquid or soft food.
40 kg to less than 120 kg	600 mg	2 tablespoons	3 Tecovirimat capsules	Mix entire contents of 3 Tecovirimat capsules with 2 tablespoons of liquid or soft food.
120 kg and above	600 mg	2 tablespoons	3 Tecovirimat capsules	Mix entire contents of 3 Tecovirimat capsules with 2 tablespoons of liquid or soft food.

If you take more Tecovirimat SIGA than you should

Let your doctor know if you take too many Tecovirimat SIGA capsules so that your doctor can monitor you for any signs or symptoms of side effects.

If you forget to take Tecovirimat SIGA

If you miss a dose, skip that dose and continue with your next scheduled dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Tecovirimat SIGA, your symptoms may return or become worse

Do not stop taking Tecovirimat SIGA before you have completed the course, or without talking to your doctor or pharmacist first.

If you vomit after taking Tecovirimat SIGA

If you vomit within 30 minutes of taking Tecovirimat SIGA, you may take another dose right away. If you vomit more than 30 minutes after taking Tecovirimat SIGA, do not take another dose and continue with your next scheduled dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Very common side effects (may affect more than 1 in 10 people)
- Headache

Common side effects (may affect up to 1 in 10 people)
- Dizziness
- Feeling sick (nausea) or vomiting
- Diarrhoea
- Abdominal pain

Uncommon side effects (may affect up to 1 in 100 people)
- Decreased appetite
- Increased liver enzymes
- Depression or anxiety
- Irritability
- Depression
- Panic attacks
- Migraine
- Feeling tired or sleepy or unable to sleep
- Being unable to concentrate or having a low attention span
- Taste disturbances
- Tingling or numbness in the hands, feet or or mouth
- Mouth pain
- Constipation
- Flatulence
- Indigestion or upset stomach
- Abdominal discomfort or swelling
- Dry mouth
- Dry or chapped lips
- Mouth ulcers
- Belching or burping

- Heartburn
- Itching or rash (hives)
- Joint pain and stiffness
- Fever
- Chills
- Generally feeling unwell (malaise)
- Pain
- Feeling thirsty
- If you have a scan of your brain's electrical activity called an electrocephalogram, it may show abnormal readings of electrical activity of the brain.
- If you have a blood test, it may show that you have lower numbers of red blood cells or white blood cells or platelets than usual.
- Increased heart rate (tachycardia) or irregular heart rate

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Tecovirimat SIGA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

Store below 25°C.

Do not use this medicine if you notice that the capsule is broken or damaged in any way.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tecovirimat SIGA contains

- The active substance is tecovirimat monohydrate equivalent to 200 mg tecovirimat
- The other ingredients are:
  Capsule core: Silica colloidal anhydrous, croscarmellose sodium (E468), hypromellose (E464), lactose monohydrate, magnesium stearate, cellulose, microcrystalline (E460) and sodium laurilsulfate (E487).
  Capsule shell: gelatin, brilliant blue FCF (E133), erythrosine (E127), sunset yellow (E110) and titanium dioxide (E171).
  Printing ink: shellac (E904), titanium dioxide (E171), isopropyl alcohol, ammonium hydroxide (E527), butyl alcohol, propylene glycol, and simeticone.

What Tecovirimat SIGA looks like and contents of the pack

- Tecovirimat SIGA are orange and black capsules, each printed with 'SIGA®' and 'ST-246' in white ink. The capsules are 21.7 millimeters long and 7.64 millimeters in diameter.
- Tecovirimat SIGA is available in a pack containing 84 (2 bottles of 42) capsules.

Marketing Authorisation Holder

SIGA Technologies Netherlands B.V.
Prinsenhil 29,
Breda 4825 AX,
The Netherlands

Manufacturer

Millmount Healthcare Limited
Block-7, City North Business Campus,
Stamullen
Co. Meath
K32 YD60
Ireland

This leaflet was last revised in

This medicine has been authorised under 'exceptional circumstances'. This means that for ethical reasons it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu