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

Dectova 10 mg/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 10 mg of zanamivir (as hydrate).

Each vial contains 200 mg of zanamivir (as hydrate) in 20 mL.

Excipients with known effect

Each vial contains 3.08 mmol (70.8 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion
Clear, colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dectova is indicated for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when:

- The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or
- Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.

Dectova should be used in accordance with official guidance.

4.2 Posology and method of administration

Posology

Treatment with Dectova should commence as soon as possible and usually within 6 days of the onset of symptoms of influenza (see section 5.1).

Adults
The recommended dose is 600 mg twice daily for 5 to 10 days given by intravenous infusion.

Paediatric population

Adolescents, children and infants should receive a weight-based dose regimen for 5 to 10 days (Table 1).

Table 1: Weight-based dose regimen by age for infants, children and adolescents with normal renal function

Age range	**Weight-based dose regimen**
6 months to < 6 years	14 mg/kg twice daily
≥ 6 years to < 18 years	12 mg/kg twice daily up to a maximum dose of 600 mg twice daily

Elderly
No dose adjustment is required based on age.

Renal impairment
Adults and children (aged 6 years and over with a body weight of 50 kg or above) with creatinine clearance (CLcr) or clearance by continual renal replacement therapy (CL_{CRRT}) < 80 mL/min should receive an initial 600 mg dose followed by twice-daily maintenance dosing according to their renal function (Table 2).

Table 2: Initial and maintenance dose regimens for adults and children (6 years and over with a body weight of 50 kg or above) with renal impairment

CLcr or CL_{CRRT} (mL/min or mL/min/1.73m^2)*	**Initial dose**	**Maintenance dose**	**Maintenance dose schedule**
50 to <80	600 mg	400 mg twice daily	Begin maintenance dosing 12 hours after the initial dose
30 to <50	600 mg	250 mg twice daily	
15 to <30	600 mg	150 mg twice daily	Begin maintenance dosing 24 hours after the initial dose
< 15	600 mg	60 mg twice daily	Begin maintenance dosing 48 hours after the initial dose

*CLcr or CL_{CRRT} units in mL/min for adolescents 13 years to less than 18 years, or in mL/min/1.73m^2 for children 6 years to less than 13 years.

Children and adolescents (6 years to less than 18 years with a body weight less than 50 kg), and infants and children (6 months to less than 6 years) with creatinine clearance (CLcr) or clearance by continual renal replacement therapy (CL_{CRRT}) <80 mL/min should receive an initial dose followed by an appropriate twice-daily maintenance dose as shown in Tables 3, 4 and 5.

Table 3: Initial and maintenance dose regimens for children and adolescents (6 years to less than 18 years, with a body weight less than 50 kg) with renal impairment

CLcr or $CL_{CRRT)}$ (mL/min or mL/min/1.73m^2)*	Initial dose	Maintenance dose	Maintenance dose schedule
50 to <80	12 mg/kg	8 mg/kg twice daily	Begin twice daily maintenance dosing 12 hours after the initial dose
30 to <50	12 mg/kg	5 mg/kg twice daily	
15 to <30	12 mg/kg	3 mg/kg twice daily	Begin twice daily maintenance dosing 24 hours after the initial dose
< 15	12 mg/kg	1.2 mg/kg twice daily	Begin twice daily maintenance dosing 48 hours after the initial dose

*CLcr or CL_{CRRT} units in mL/min for adolescents 13 years to less than 18 years, or in mL/min/1.73m^2 for children 6 years to less than 13 years.

Table 4: Initial and maintenance dose regimens for infants and children (6 months to less than 6 years, with a body weight of 42.8 kg or above) with renal impairment

CLcr or CL_{CRRT} (mL/min/1.73 m^2)	Initial dose	Maintenance dose	Maintenance dose schedule
50 to <80	600 mg	400 mg twice daily	Begin twice daily maintenance dosing 12 hours after the initial dose
30 to <50	600 mg	250 mg twice daily	
15 to <30	600 mg	150 mg twice daily	Begin twice daily maintenance dosing 24 hours after the initial dose
< 15	600 mg	60 mg twice daily	Begin twice daily maintenance dosing 48 hours after the initial dose

Table 5: Initial and maintenance dose regimens for infants and children (6 months to less than 6 years, with a body weight less than 42.8 kg) with renal impairment

CLcr or CL_{CRRT} (mL/min/1.73 m^2)	Initial dose	Maintenance dose	Maintenance dose schedule
50 to <80	14 mg/kg	9.3 mg/kg twice daily	Begin twice daily maintenance dosing 12 hours after the initial dose
30 to <50	14 mg/kg	5.8 mg/kg twice daily	
15 to <30	14 mg/kg	3.5 mg/kg twice daily	Begin twice daily maintenance dosing 24 hours after the initial dose
< 15	14 mg/kg	1.4 mg/kg twice daily	Begin twice daily maintenance dosing 48 hours after the initial dose

For patients on intermittent haemodialysis or intermittent peritoneal dialysis, the dose should be given after completion of the dialysis session.

For patients receiving continuous renal replacement therapy, the dose should be selected using the appropriate CRRT clearance (CL_{CRRT} in mL/min).

Hepatic impairment
No dose modification is required (see section 5.2).

Paediatric population
The safety and efficacy of Dectova in children aged under 6 months have not been established. No data are available.

Method of administration

Intravenous use

Dectova is administered by intravenous infusion over 30 minutes.

For instructions on dilution of the medicinal product before administration, see section 6.6.

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

Renal impairment

Zanamivir is eliminated by renal clearance, therefore the dose of Dectova when administered intravenously must be reduced in patients with renal impairment (see section 4.2). All patients must have their renal function assessed before and regularly during treatment.

Serious hypersensitivity reactions

Anaphylactic reactions and serious skin reactions (including erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported with zanamivir (see section 4.8). If any hypersensitivity reaction occurs during infusion of Dectova, the infusion must be stopped immediately and appropriate management should be instituted.

Neuropsychiatric events

Influenza can be associated with a variety of neurological and behavioural symptoms. Neuropsychiatric events, including seizures, delirium, hallucination and abnormal behaviour, have been reported during administration of zanamivir in patients with influenza, especially in children and adolescents. Therefore, patients should be closely monitored for behavioural changes and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

Resistance in immunocompromised patients

Treatment emergent resistance is rare with zanamivir (see section 5.1). Selection of influenza resistant viruses is more likely to occur following treatment with antiviral medicinal products in immunocompromised patients, including treatment with Dectova; it is, therefore, important to monitor for resistance and consider switching to alternative therapies where appropriate.

Limitations of the clinical data

The efficacy of Dectova for the treatment of complicated influenza A or B virus infection in adults and children aged from 6 months has been inferred from:

- the *in vitro* activity of zanamivir;
- clinical and virological activity of zanamivir compared to placebo in a human influenza challenge study;
- levels of zanamivir in broncho-epithelial lining fluid and serum zanamivir from a broncho-alveolar lavage study;
- serum zanamivir levels from patients with complicated influenza (see section 5.1).

Risk of bacterial infections

Dectova has not been shown to reduce the risk of bacterial complications associated with influenza infection.

Excipients

This medicinal product contains 70.8 mg sodium per vial, equivalent to 3.54% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

The potential for interactions with other medicines is low, based on the known elimination pathway of zanamivir.

Zanamivir is not a substrate, inhibitor or inducer of cytochrome P450 isoenzymes nor a substrate or inhibitor of renal and hepatic transporters at clinically relevant concentrations (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of zanamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs and there was no evidence of teratogenicity. Results from a rat peri- and postnatal study showed no clinically meaningful impairment of offspring development. However, there is no information on placental transfer in humans.

As experience is limited, the use of Dectova in pregnancy should only be considered if the possible benefit to the patient is thought to outweigh any possible risk to the foetus.

Breast-feeding

It is unknown whether zanamivir is excreted in human milk. In rats, zanamivir has been shown to be secreted in low amounts into milk.

As experience is limited, the use of zanamivir in breast-feeding mothers should be considered only if the possible benefit to the mother is thought to outweigh any possible risk to the child.

Fertility

Animal studies indicate no clinically meaningful effects of zanamivir on male or female fertility.

4.7 Effects on ability to drive and use machines

Zanamivir has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of zanamivir is based primarily on data from a single Phase II and a single Phase III study, with support from Phase I studies, a compassionate use programme, and adverse drug reactions reported for inhaled zanamivir. The frequency of adverse reactions is based on the number of reports in the adult population receiving zanamivir 600 mg twice daily intravenously in the Phase II and Phase III studies. Adverse reactions are listed by MedDRA system organ class.

The most commonly reported adverse reactions considered possibly or probably related to zanamivir are alanine aminotransferase increased (2%), aspartate aminotransferase increased (1%), hepatocellular injury (1%), diarrhoea (1%) and rash (1%). The most important serious adverse reaction was hepatocellular injury, observed in two patients (<1%).

Tabulated list of adverse reactions

The frequency of adverse reactions is defined using the following convention: 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 available data).

System Organ Class	Adverse reactions	Frequency
Immune system disorders	oropharyngeal oedema facial oedema anaphylactic/anaphylactoid reactions	not known
Psychiatric disorders	abnormal behaviour hallucinations delirium	not known
Nervous system disorders	convulsions depressed level of consciousness	not known
Gastrointestinal disorders	diarrhoea	common
Hepatobiliary disorders	alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) increased hepatocellular injury	common
	alkaline phosphatase increased	uncommon
Skin and subcutaneous tissue disorders	rash	common
	urticaria	uncommon
	erythema multiforme Stevens-Johnson syndrome toxic epidermal necrolysis	not known

Paediatric population

The adverse reaction profile in the paediatric population is based on 71 patients aged ≥6 months to <18 years in the Phase II study. Overall, the safety profile in paediatric patients was similar to that observed in adults in the clinical studies.

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

There is limited experience of overdose from administration of Dectova. There is no specific antidote to treat an overdose of this medicine. Treatment of an overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Zanamivir is cleared by renal excretion and is expected to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors
ATC code: J05AH01

Mechanism of action

Zanamivir is an inhibitor of influenza virus neuraminidase, an enzyme that releases viral particles from the plasma membrane of infected cells and promotes virus spread in the respiratory tract.

In vitro activity

Neuraminidase inhibition occurred at very low zanamivir concentrations *in vitro*, with median inhibitory (IC_{50}) values of 0.33 nM to 5.77 nM against influenza A and B strains respectively.

Resistance
Resistance selection during zanamivir treatment is rare. Reduced susceptibility to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Neuraminidase substitutions conferring reduced susceptibility to zanamivir have emerged during treatment with zanamivir in human viruses and those with zoonotic potential: E119D, E119G, I223R, R368G, G370D, N434S (A/H1N1); N294S, T325I (A/H3N2); R150K (B); R292K (A/H7N9). The neuraminidase substitution Q136K (A/H1N1 and A/H3N2), confers high level resistance to zanamivir but is selected during adaptation to cell culture and not during treatment.

The clinical impact of reduced susceptibility in these viruses is unknown, and the effects of specific substitutions on virus susceptibility to zanamivir may be strain-dependent.

Cross-resistance
Cross-resistance between zanamivir and oseltamivir or peramivir has been observed in neuraminidase inhibition assays. A number of neuraminidase amino acid substitutions that arise during oseltamivir or peramivir treatment result in reduced susceptibility to zanamivir. The clinical impact of substitutions associated with reduced susceptibility to zanamivir and other neuraminidase inhibitors is variable and may be strain-dependent.

The H275Y substitution is the most common neuraminidase resistance substitution and is associated with reduced susceptibility to peramivir and oseltamivir. This substitution has no effect on zanamivir; therefore, viruses with the H275Y substitution retain full susceptibility to zanamivir.

Clinical efficacy

Human challenge study
A double-blind, randomised study to examine the prophylactic antiviral activity and efficacy of repeat dose zanamivir 600 mg every 12 hours intravenously compared to placebo in healthy male volunteers against infection from inoculation with influenza A/Texas/91 (H1N1) virus was conducted. Zanamivir had a significant prophylactic effect against an experimental challenge with influenza A virus as demonstrated by the low infection rate (14% vs. 100% positive serology in placebo group, $p < 0.005$), isolation of virus by viral culture (0% vs. 100% in placebo group, $p < 0.005$), as well as reductions in fever (14% vs. 88% in placebo group, $p < 0.05$), upper respiratory tract illness (0% versus 100% in placebo group, $p < 0.005$) and total symptom scores (1 vs. 44 median score in placebo group, $p < 0.001$).

Bronchoalveolar lavage study
A Phase I, open-label study to evaluate serum and lower respiratory pharmacokinetics following administration of intravenous and inhaled zanamivir to healthy adult subjects utilising bronchoalveolar lavage fluid was conducted. The 600 mg dose given intravenously best approximated epithelial lining fluid concentrations achieved by the approved 10 mg dose of zanamivir inhalation powder which demonstrated efficacy in large clinical studies in uncomplicated influenza.

Phase III study in patients with complicated influenza
A Phase III, double-blind, study was conducted to evaluate the efficacy, antiviral activity and safety of zanamivir 600 mg twice daily intravenously compared to oral oseltamivir 75 mg twice daily and 300 mg zanamivir twice daily intravenously in hospitalised patients (>16 years of age) with influenza. The median patient age was 57 years and 35% (218/615) of patients were ≥65 years, of which 17% (n=103) were 65 to <75; 14% (n=84) were 75 to <85, and 5% (n=31) were ≥85 years of age. Patients were stratified at randomisation based on time from onset of symptoms to initiation of treatment (≤4 days and 5 to 6 days). Eligible patients were not to have had >3 days of prior antiviral treatment. The initial 5 day treatment course could be extended for up to 5 additional days if clinical symptoms or patient characteristics warranted further treatment. The primary endpoint was time to clinical response (TTCR); clinical response was defined as a composite of vital sign stabilisation (temperature, oxygen saturation, respiratory status, heart rate and systolic blood pressure) or hospital discharge. The primary analysis was performed on the Influenza Positive Population (IPP) comprised of 488 patients. The study did not meet its pre-specified primary objective of demonstrating superiority of 600 mg zanamivir to oral oseltamivir or to 300 mg zanamivir in TTCR. There were no significant differences in TTCR across treatment comparisons in the overall IPP or in two pre-specified subgroups (Table 6).

Table 6: Statistical comparisons of TTCR between the 600 mg zanamivir group and each other group (IPP)

	Zanamivir solution for infusion 300 mg	**Zanamivir solution for infusion 600 mg**	**Oseltamivir 75 mg**
Influenza Positive Population, N	163	162	163
Median TTCR, days	5.87	5.14	5.63
Median difference between treatments, days (95% CI)	-0.73 (-1.79, 0.75)		-0.48 (-2.11, 0.97)
p-value from Wilcoxon rank-sum 2-sided test	0.25		0.39
Intensive Care Unit/Mechanical Ventilation subgroup, N	68	54	68
Median TTCR, days	11.26	12.79	14.58
Median difference between treatments, days (95% CI)	1.53 (-4.29, 8.34)		-1.79 (-11.1, 6.92)
p-value from Wilcoxon rank-sum 2-sided test	0.87		0.51
Symptom onset ≤4 days subgroup, N	127	131	121
Median TTCR, days	5.63	4.80	4.80
Median difference between treatments, days (95% CI)	-0.83 (-1.98, 0.56)		0.00 (-1.05, 0.97)
p-value from Wilcoxon rank-sum 2-sided test	0.09		0.82

This medicinal product has been authorised under 'exceptional circumstances'.
This means that for scientific 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Dectova in one or more subsets of the paediatric population in the treatment and prevention of influenza (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The serum pharmacokinetics of zanamivir administered intravenously have been studied in healthy volunteers receiving single escalating doses from 1 to 1200 mg and repeated doses of 600 mg twice daily for 5 days. Hospitalised patients with influenza also have received 300 mg or 600 mg twice daily for 5 to 10 days.

Dose proportionality was observed in zanamivir C_{max} and AUC and no accumulation of zanamivir in serum was evident after repeated intravenous doses of up to 600 mg.

Distribution

The plasma protein binding of zanamivir is very low (less than 10%). The volume of distribution of zanamivir in adults is approximately 16 litres, which approximates the volume of extracellular water.

Following twice-daily administration of zanamivir solution for infusion, pulmonary epithelial lining fluid concentrations were 60 - 65 % of the serum concentrations at the corresponding sampling time 12 hours after dosing. Following twice daily administration of 600 mg zanamivir solution for infusion, median trough zanamivir epithelial lining fluid concentrations ranged from 419 ng/mL to 584 ng/mL and were 47-66% of those in the initial bronchoalveolar sample following orally zanamivir inhalation powder 10 mg twice daily.

In vitro studies indicate that zanamivir is not an inhibitor or substrate of Breast Cancer Resistant Protein (BCRP), P-glycoprotein, Multidrug And Toxin Extrusion protein (MATE)1, MATE2-K, Organic Anion

Transporter (OAT)1, OAT3, Organic Anion Transporting Polypeptide (OATP)1B1, OATP1B3 and Organic Cation Transporter (OCT)2 transporters.

Biotransformation

There is no evidence that zanamivir is metabolised.

Zanamivir is not an inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4. Zanamivir is not an inducer of CYP1A2 and 2B6 and, although induction of CYP3A4 *in vitro* was observed at 50-fold higher than the clinically relevant concentrations, no interaction with CYP3A4 substrates is expected based on physiologically based pharmacokinetic modelling.

Elimination

Zanamivir is eliminated unchanged in urine by glomerular filtration. In adults with normal renal function, the elimination half-life is approximately 2-3 hours.

Elderly

The pharmacokinetics in elderly subjects was similar to young adult subjects. In the population pharmacokinetic analysis, age had no significant effect on the pharmacokinetics of zanamivir.

Paediatric population

The pharmacokinetics of zanamivir following a twice daily intravenous dose of 14 mg/kg for paediatric patients between 6 months and <6 years and 12 mg/kg for those between 6 years and <18 years of age were similar to those seen in adults who received 600 mg twice daily intravenously. The pharmacokinetics of zanamivir in subjects 6 months to <18 years of age (administered standard dose of 12 mg/kg, 14 mg/kg or 600 mg according to age and body weight) and in adult subjects (administered standard dose of 600 mg) was similar (Table 7).

Table 7: Pharmacokinetic parameters in paediatric and adult subjects

Age Group	Dose	N	C_{max} (µg/mL)		AUC(0-∞) (µg.h/mL)		C_{min} (µg/mL)		$T_{1/2}$ (h)	
			GM	%CV	GM	%CV	GM	Range	GM	%CV
6 months - <1 year	14 mg/kg	7	36.2	21	75.3	23	NA	NA	1.84	19
1 - <2 years	14 mg/kg	6	37.8	24	72.4	14	0.305	NA	2.49	118
2 - <6 years	14 mg/kg	12	41.5	23	80.3	38	0.277	0.133 – 0.984	1.60	34
6 - <13 years	12 mg/kg	16	44.2	47	107	41	0.564	0.111 – 2.31	2.57	55
13 - <18 years	600 mg	13	34.5	27	91.1	27	0.211	0.104 – 0.428	2.06	47
>18 years	600 mg	67	32.8	34	82.9	36	0.82	0.1 - 11.4	2.39	31

%CV = percent coefficient of variation, GM = Geometric Mean, NA = Not available

Renal impairment

The serum half-life of zanamivir increases to approximately 12-20 hours in patients with severe renal impairment (creatinine clearance < 30 mL/min). Dectova has not been studied in patients with end-stage renal disease.

There are limited data on zanamivir exposure during concomitant continuous renal replacement therapy and very limited data with dialysis.

Hepatic impairment

Zanamivir is not metabolised, therefore no effect of hepatic impairment is expected.

Race

Pharmacokinetic studies in Thai, Chinese and Japanese healthy subjects did not identify any clinically relevant differences in the pharmacokinetics of zanamivir in these populations compared with Caucasians.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction and development, with the exception of a rat embryofoetal development study (subcutaneous administration). In the rat embryofoetal study, there was an increase in the incidence rates of a variety of minor skeletal and visceral alterations, most of which remained within the background rates of the historical occurrence in the strain studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

Dectova must not be mixed with other medicinal products except those mentioned in section 6.6.

Dectova should not be administered simultaneously with other intravenous medicinal products or prepared in solutions containing glucose or other electrolytes (see section 6.6).

6.3 Shelf life

Unopened vials

5 years.

After dilution

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2ºC to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

26 mL clear vial (type I glass) with a stopper (coated chlorobutyl rubber), an over-seal (aluminium) and a plastic flip-off cap.

Pack size: 1 vial.

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.

Preparation of Dectova

- The volume of Dectova and total volume for infusion will depend on the patient's age, weight and renal function (see section 4.2).
- The dose can be infused as supplied or diluted in sodium chloride 9 mg/mL (0.9%) solution for injection down to any concentration greater than or equal to 0.2 mg/mL.
- Each vial is for single use only; once the seal has been broken, the remaining volume must be discarded.

How to prepare the infusion for intravenous administration:

- Use aseptic techniques throughout preparation of the dose.
- Calculate the required dose and volume of Dectova.
- Decide on the volume of sodium chloride 9 mg/mL (0.9%) solution for injection to be used for infusion.
- Using a sterile needle and syringe, withdraw and discard a volume of sodium chloride 9 mg/mL (0.9%) solution for injection (equal to the volume of Dectova) from the infusion bag.
- Infusion bags may have a further overage of sodium chloride 9 mg/mL (0.9%) solution for injection included – this can also be removed if considered necessary.
- Using a sterile needle and syringe withdraw the volume of Dectova from the vial(s) and add to the infusion bag.
- Discard any unused portion of the vial.
- The infusion bag should be gently manipulated by hand to ensure it is mixed thoroughly.
- If refrigerated, the infusion bag should be removed from the refrigerator and brought up to room temperature before use.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1349/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 April 2019
Date of latest renewal:

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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana No. 90
43056 San Polo di Torrile, Parma
Italy

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**

The requirements for submission of periodic safety update reports 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.

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

- **Risk Management Plan (RMP)**

The 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 a marketing authorisation under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with complicated influenza infection	Annual reports to be submitted

Description	Due date
In order to evaluate the clinical effectiveness of treatment with zanamivir 10mg/ml solution for infusion in ICU-treated influenza patients, the MAH should submit the results of an observational chart review effectiveness study of IV zanamivir in ICU-treated influenza patients.	Q3 2025
A prospective observational study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in patients with complicated influenza infection In order to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in patients with complicated influenza infection, the MAH should submit the results of a prospective observational study in patients with complicated influenza infection.	Annual reports to be submitted

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dectova 10 mg/mL solution for infusion
zanamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 200 mg of zanamivir (as hydrate) in 20 mL (10 mg/mL).

3. LIST OF EXCIPIENTS

Also contains sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
200 mg/20 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.
For single use only.

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

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

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1349/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dectova 10 mg/mL solution for infusion
zanamivir
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/20 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Dectova 10 mg/mL solution for infusion
zanamivir

▼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 are given 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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dectova is and what it is used for

Dectova contains zanamivir, which belongs to a group of medicines called antivirals.
Dectova **is used to treat severe flu** (influenza A or B virus infection). It is used when other flu treatments are not suitable.
Adults and children aged 6 months or more can be treated with Dectova.

2. What you need to know before you are given Dectova

Do not use Dectova:
- **if you are allergic** to zanamivir or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Serious skin or allergic reactions

Serious skin or allergic reactions may occur after Dectova is given. Symptoms may include skin or throat swelling, difficulty breathing, blistering rash or peeling skin (see also '*Serious skin or allergic reactions*' in section 4).

Sudden changes in behaviour, hallucinations and fits

During treatment with Dectova, changes in behaviour such as confusion and unresponsiveness may occur. Some people may also have hallucinations (seeing, hearing, or feeling things that are not there) or fits (seizures) which can lead to loss of consciousness. These symptoms also occur in people with flu who are not being given Dectova. So it is not known if Dectova played a part in causing them.

If you are immunocompromised (have a weakened immune system)

Your doctor may monitor you more closely if your immune system is not working properly to ensure the treatment is working. Your doctor may switch you to an alternative treatment where appropriate.

If you notice any of the above symptoms:

➔ **Tell a doctor or nurse immediately.**

Other medicines and Dectova
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, **ask your doctor for advice before you are given this medicine.**

Driving and using machines
Dectova should not affect your ability to drive or use machines.

Dectova contains sodium
This medicine contains 70.8 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 3.54% of the recommended maximum daily intake of sodium for an adult.

3. How Dectova is given

How much Dectova is given
Your doctor will decide how much Dectova is right for you. The amount you are given is based on your age, body weight, and the results of your blood tests (to check how well your kidneys are working).

Your dose may be increased or decreased depending on how well you respond to treatment.

Adults
The recommended dose is 600 mg twice daily for 5 to 10 days.

If your kidneys are not working as well as they should, your doctor will decide on the reduced dose for you.

Children
Your doctor will decide on the correct dose of Dectova.

When and how Dectova is given
Dectova should be given as soon as possible, usually within 6 days of the symptoms of flu appearing.

A doctor or nurse will give you Dectova as an infusion (drip) into a vein. It is usually given into your arm over about 30 minutes.

If you have any questions on the use of Dectova, ask the doctor or nurse who is giving it you.

If you are given more Dectova than you should
It is unlikely that you will be given too much, but if you think you have been given too much Dectova, **tell your doctor or nurse immediately.**

4. Possible side effects

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

Serious skin and allergic reactions may occur with Dectova, but there isn't enough information to estimate how likely they are. Contact your doctor or nurse straight away if you notice any of the following serious side effects:

- very severe skin reactions such as:
    - a skin rash, which may blister, and looks like small targets (erythema multiforme)
    - a widespread rash with blisters and peeling skin, particularly occurring around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
    - extensive peeling of the skin on much of the body surface (toxic epidermal necrolysis).
- severe allergic reactions, including features such as itchy rash, swelling of the face, throat or tongue, breathing difficulty, light headedness and vomiting.

Common side effects
These may affect **up to 1 in 10** people

- diarrhoea
- liver damage (hepatocellular injury)
- rash.

Common side effects that may show up in your blood tests:

- increase in the level of liver enzymes (raised aminotransferases).

Uncommon side effects
These may affect up to **1 in 100** people

- itchy, bumpy rash (hives).

Uncommon side effects that may show up in your blood tests:

- increase in the level of liver or bone enzymes (raised alkaline phosphatase).

Side effects where it is not known how likely they are to happen
There isn't enough information to estimate how likely these side effects are:

- acting strangely
- seeing, hearing or feeling things which are not there
- confused thinking
- fits (seizures)
- being less alert or not responding to loud sounds or being shaken

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. 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 Dectova

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 carton and vial after EXP.

Vials of Dectova are for single use only. Any unused solution should be discarded.

6. Contents of the pack and other information

What Dectova contains
The active substance is zanamivir.

Each mL of Dectova contains 10 mg of zanamivir (as hydrate). Each vial contains 200 mg of zanamivir (as hydrate) in 20 mL.
Other ingredients are sodium chloride and water for injections.

What Dectova looks like and contents of the pack
Dectova is a clear, colourless solution for infusion. It is supplied in a 26 mL clear glass vial with a rubber stopper and an aluminium over-seal with a plastic flip off cap.

There is 1 vial in each pack.

Marketing Authorisation Holder
GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer
GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana, 90
43056 San Polo di Torrile
Parma
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 (0) 10 85 52 00

България
GlaxoSmithKline Trading Services Limited
Тел.: +359 80018205

Česká republika
GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Danmark
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Eesti
GlaxoSmithKline Trading Services Limited
Tel: +372 8002640

Lietuva
GlaxoSmithKline Trading Services Limited
Tel: +370 80000334

Luxembourg/Luxemburg
GlaxoSmithKline Pharmaceuticals s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 52 00

Magyarország
GlaxoSmithKline Trading Services Limited
Tel.: +36 80088309

Malta
GlaxoSmithKline Trading Services Limited
Tel: +356 80065004

Nederland
GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Ελλάδα
GlaxoSmithKline Μονοπρόσωπη A.E.B.E.
Τηλ: + 30 210 68 82 100

España
GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

France
Laboratoire GlaxoSmithKline
Tél: + 33 (0)1 39 17 84 44
diam@gsk.com

Hrvatska
GlaxoSmithKline Trading Services Limited
Tel: +385 800787089

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 7741 111

Κύπρος
GlaxoSmithKline Trading Services Limited
Τηλ: +357 80070017

Latvija
GlaxoSmithKline Trading Services Limited
Tel: +371 80205045

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline Trading Services Limited
Tel: +40 800672524

Slovenija
GlaxoSmithKline Trading Services Limited
Tel: +386 80688869

Slovenská republika
GlaxoSmithKline Trading Services Limited
Tel: +421 800500589

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom (Northern Ireland)
GlaxoSmithKline Trading Services Limited
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

This leaflet was last revised in {month YYYY}.

This medicine has been authorised under 'exceptional circumstances'.
This means that for scientific reasons it has not been possible 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

The following information is intended for healthcare professionals only:

7. INFORMATION FOR HEALTHCARE PROFESSIONALS

Dectova preparation

- The volume of Dectova and total volume for infusion will depend on the patient's age, weight and renal function (see section 4.2 of the SmPC).
- The dose can be infused as supplied or diluted in sodium chloride 9 mg/mL (0.9%) solution for injection down to any concentration greater than or equal to 0.2 mg/mL.
- Each vial is for single use only; once the seal has been broken, the remaining volume must be discarded.

How to prepare the infusion for intravenous administration:

- Use aseptic techniques throughout preparation of the dose.
- Calculate the required dose and volume of Dectova.
- Decide on the volume of sodium chloride 9 mg/mL (0.9%) solution for injection to be used for infusion.
- Using a sterile needle and syringe, withdraw and discard a volume of sodium chloride 9 mg/mL (0.9%) solution for injection (equal to the volume of Dectova) from the infusion bag.
- Infusion bags may have a further overage of sodium chloride 9 mg/mL (0.9%) solution for injection included – this can also be removed if considered necessary.
- Using a sterile needle and syringe, withdraw the volume of Dectova from the vial(s) and add to the infusion bag.
- Discard any unused portion of the vial.
- The infusion bag should be gently manipulated by hand to ensure it is mixed thoroughly.
- If refrigerated, the infusion bag should be removed from the refrigerator and brought up to room temperature before use.