Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Zanamivir

RMP version to be assessed as part of this application	
RMP Version number	8.2
Data lock point for this RMP	31 Jan 2024
Date of final sign off	20 Nov 2024

Rationale for submitting an updated RMP

This EU-RMP for zanamivir has been updated following discontinuation of Zanamivir pregnancy registry as per the outcome of EMEA/H/C/004102/MEA/003.2.

Summary of significant changes in this RMP:

This EU-RMP for zanamivir has been updated following discontinuation of Zanamivir pregnancy registry study (PASS) upon receipt of outcome of EMEA/H/C/004102/MEA/003.2. The revisions include the following:

Removal of Pregnancy Registry study following outcome of EMEA/H/C/004102/MEA/003.2

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PART	MODULE	Changes made in the present EU-RMP
I	Table 1 and Table 2	Information of indication, dosage in the EEA, Pharmaceutical form (s) and strengths were moved from proposed to current and minor changes are made
II	Module SI , Module SI.1.2	Table 3, Table 4 and Table 6 are updated to reflect current epidemiological data and minor editorial updates are made New data on existing treatment options is updated
II	Module SIII	Clinical trial exposure data was updated in Table 8,Table 9, Table 10 and Table 11
II	Module SIV	Minor editorial updates
II	Module SV.1	Post Authorization exposure details, minor editorial changes are done
II	Module SVI	Minor update
III	Part III.2	Pregnancy registry information was removed for IV zanamivir
III	Part III.3	Pregnancy registry information was removed from ongoing and planned additional pharmacovigilance activities.

IV	Part IV	Status of efficacy studies was updated in Table 15
VI	Part VI	Minor editorial changes are made
VI	Part II.B, Part II. C.2	Summary was updated
VII	Annex 2	Pregnancy registry details are added in completed studies list
VII	Annex 5	Ongoing studies list and status is updated

Other RMP versions under evaluation

Not applicable

RMP Version number	Submitted on	Procedure number
NA	NA	NA

Details of the currently approved RMP

Not applicable

Version number	Approved with procedure	Date of approval (opinion date)
7.0	Centralised Procedure: EMEA/H/C/4102/0000	26 Apr 2019

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety and Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ASI	Area of Special Interest
AST	Aspartate Transaminase
CHMP	Committee for Medicinal Products for Human Use
CUP	Compassionate Use Programme
ECDC	European Centre for Disease Prevention and Control
eCRF EEA	Electronic case report form European Economic Area
EMA	European Medicines Agency
EM	Erythema Multiforme
HCP	Healthcare Professional
HDU	High Dependency Unit
ICU	Intensive Care Unit
IV zanamivir	Zanamivir 10mg/ml solution for infusion
Inhaled zanamivir	Zanamivir 5mg powder for inhalation influenza
A(H1N1)pdm09	Influenza A H1N1 pandemic 2009 virus
INC	Influenza-related neurological complication
NA	Neuraminidase
NAI	Neuraminidase inhibitor
PAES	Post-authorisation Efficacy Study
PASS	Post-authorisation Safety Study
PIL	Patient Information Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
RMM	Risk Minimisation Measure
aRMM	Additional Risk Minimisation Measure
RKI	Robert Koch Institute
SAE	Serious Adverse Event
SARI	Severe acute respiratory infection
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SOC	System Organ Class
S-PSUR	Simplified PSUR
TEN	Toxic Epidermal Necrolysis
ULN	Upper Limit of Normal
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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RELENZA

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PART I: PRODUCT(S) OVERVIEW

Note: Product Overview is presented in separate tables for DECTOVA and RELENZA

Table 1 Product Overview for DECTOVA

Active substance(s) **(INN or common name)**	Zanamivir
Pharmacotherapeutic group(s) (ATC Code)	J05AH01
Marketing Authorization Holder/ Applicant	GlaxoSmithKline Trading Services Limited
Medicinal products to which this RMP refers	Zanamivir 10mg/ml solution for infusion (IV zanamivir)
Invented name(s) in the European Economic Area (EEA)	DECTOVA
Marketing authorization procedure	Centralised Procedure
Brief description of the product	Chemical class Neuraminidase inhibitor
	Summary of mode 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. The activity of zanamivir is extracellular. It reduces the propagation of both influenza A and B viruses by inhibiting the release of infectious influenza virions from the epithelial cells of the respiratory tract. Influenza viral replication is confined to the superficial epithelium of the respiratory tract.
	Important information about its composition 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.
Reference to the Product Information	Please refer to the Product Information (section 1.3.1 of the eCTD).
Indication(s) in the EEA	Current: 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.
Dosage in the EEA	Current: Treatment with Dectova should commence as soon as possible and usually within 6 days of the onset of symptoms of influenza. Dectova is administered by intravenous infusion over 30 minutes. The recommended dose is 600 mg twice daily for 5 to 10 days given by intravenous infusion. Adolescents, children and infants should receive a weight-based dose regimen for 5 to 10 days. 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.
Pharmaceutical form(s) and strengths	Current: 10mg/ml solution for infusion; a clear, colourless solution for infusion.
Is/will the product be subject to additional monitoring in the EU?	Yes

Table 2 Product Overview for RELENZA

Active substance(s) **(INN or common name)**	Zanamivir
Pharmacotherapeutic group(s) (ATC Code)	J05AH01
Marketing Authorization Holder/ Applicant	GlaxoSmithKline AB (Sweden – Reference Member State)
Medicinal products to which this RMP refers	Zanamivir powder for inhalation (5mg)
Invented name(s) in the European Economic Area (EEA)	RELENZA
Marketing authorization procedure	Mutual Recognition Procedure
Brief description of the product	Chemical class Neuraminidase inhibitor
	Summary of mode 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. The activity of zanamivir is extracellular. It reduces the propagation of both influenza A and B viruses by inhibiting the release of infectious influenza virions from the epithelial cells of the respiratory tract. Influenza viral replication is confined to the superficial epithelium of the respiratory tract. The efficacy of topical administration of zanamivir to this site has been confirmed in clinical studies. Clinical trial data have shown that treatment of acute influenza infections with zanamivir produces reductions in virus shedding from the respiratory tract compared to placebo without any detectable emergence of virus with reduced susceptibility to zanamivir.
	Important information about its composition 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.
Reference to the Product Information	Please refer to the approved product information.
Indication(s) in the EEA	Current: **Treatment of influenza** Relenza is indicated for treatment of both influenza A and B in adults and children (≥ 5 years) who present with symptoms typical of influenza when influenza is circulating in the community. **Prevention of influenza** Relenza is indicated for post-exposure prophylaxis of influenza A and B in adults and children (≥ 5 years) following contact with a clinically diagnosed case in a household. In exceptional circumstances, Relenza may be considered for seasonal prophylaxis of influenza A and B during a community outbreak (e.g. in case of a mismatch between circulating and vaccine strains and a pandemic situation). Relenza is not a substitute for influenza vaccination. The appropriate use of Relenza for prevention of influenza should be determined on a case-by-case basis depending on the circumstances and the population requiring protection. The use of antivirals for the treatment and prevention of influenza should take into consideration official recommendations, the variability of epidemiology, and the impact of the disease in different geographical areas and patient populations.

Dosage in the EEA	Current: **Treatment of influenza** The recommended dose of Relenza for treatment of influenza in adults and children from the age of 5 years is two inhalations (2 x 5 mg) twice daily for five days, providing a total daily inhaled dose of 20 mg. Treatment should begin as soon as possible, within 48 hours after onset of symptoms for adults, and within 36 hours after onset of symptoms for children. Relenza is for administration to the respiratory tract by oral inhalation only, using the Diskhaler device provided. One blister should be used for each inhalation. **Prevention of influenza** <u>Post-exposure prophylaxis</u> The recommended dose of Relenza for prevention of influenza, following close contact with an individual, is two inhalations (2 x 5 mg) once daily for 10 days. Therapy should begin as soon as possible and within 36 hours of exposure to an infected person. <u>Seasonal prophylaxis</u> The recommended dose of Relenza for prevention of influenza during a community outbreak is 2 inhalations (2 x 5 mg) once daily for up to 28 days. Impaired Renal or Hepatic Function: No dose modification is required. Elder patients: No dose modification is required.
Pharmaceutical form(s) and strengths	Current: 5mg, inhalation powder, pre-dispensed. White to off-white powder.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Indication

DECTOVA (zanamivir) 10mg/ml solution for infusion

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.

RELENZA (zanamivir) 5mg powder for inhalation

Treatment of influenza

Relenza is indicated for treatment of both influenza A and B in adults and children (aged 5 years and older) who present with symptoms typical of influenza when influenza is circulating in the community.

Prevention of influenza

Relenza is indicated for post-exposure prophylaxis of influenza A and B in adults and children (≥ 5 years) following contact with a clinically diagnosed case in a household. In exceptional circumstances, Relenza may be considered for seasonal prophylaxis of influenza A and B during a community outbreak (e.g., in case of a mismatch between circulating and vaccine strains and a pandemic situation).

INCIDENCE

Patients with influenza infection may present in the primary care setting with an acute uncomplicated illness of the upper respiratory tract, or a more severe complicated disease requiring secondary care (including intensive care). Complicated influenza infection is defined by the need for hospitalisation for clinical management of these symptoms and signs of lower respiratory tract infection, as well as central nervous system involvement, severe dehydration, and other secondary complications, and/or exacerbation of underlying chronic diseases such as congestive heart failure, coronary artery disease, COPD and asthma [WHO, 2010].

Zanamivir products may be used in both uncomplicated (zanamivir powder for inhalation) and complicated (zanamivir powder for inhalation and zanamivir 10mg/ml solution for infusion) influenza depending on the patient status and resistance profile of the circulating or infecting

virus. Therefore, epidemiological information is presented for both uncomplicated and complicated influenza.

Uncomplicated influenza

Influenza remains an important disease, with outbreaks every winter causing significant morbidity and mortality. It is estimated that, each year, influenza infects approximately ten to thirty per cent of Europe's population [ECDC, 2024]. In general, the incidence of influenza is highest amongst children and young adults, with the resulting absenteeism from school and the work environment placing a considerable burden on individuals and society; older age increases the likelihood of residual cross- immunity from previous influenza infections. Influenza is associated with a significant burden in terms of primary care consultations, use of antibiotics and over the counter medications.

As most respiratory viral infections are treated in general practice, many countries including those in the European Union have surveillance networks in place based around primary care sentinel practices. Consultation rates for influenza-like illness (ILI) provide an indirect assessment of circulating influenza. In England, winter weekly rates typically peak at around 20 consultations per 100,000 population (Table 3 [UKHSA, 2024]). In Wales, consultation rates are generally similar. Consultation rates in excess of 200 and 100 consultations per 100,000 population in England and Wales respectively, are considered above average.

Table 3 Seasonal peaks in general practice consultations for influenza-like illness (England) and Influenza (Wales), 2015/16 to 2022/23.

Season	Rate per 100,000 population	
	England	Wales
2015/16	28.7	26.1
2016/17	20.3	24.7
2017/18	54.1	74.5
2018/19	23.1	22.8
2019/20	19.4	37.1
2022/23	31.3	39.1

*, Seasons 2020/21 and 2021/22 omitted due to the impact of the COVID-19 pandemic on influenza

Complicated influenza

The severity of influenza depends on the antigenic composition of the virus, the extent of pre-existing population immunity and host characteristics. Patients of all ages can be hospitalised with complicated influenza. Influenza is frequently under-diagnosed in the acute care hospital setting , as clinical presentations are diverse and can be complex, especially in adults [Falsey, 2007; Rothberg, 2003]. Hospital surveillance of complicated influenza was initiated in several European countries subsequent to the 2009/10 pandemic to describe the epidemiology of severe influenza in this setting and to monitor the impact. Data from England demonstrate that considerable variation in the incidence of complicated influenza can occur both between

and within seasons, with the latter adding considerably to healthcare resource utilisation at this time of year (Table 4) [UKHSA, 2024].

Table 4 Cumulative and peak influenza hospital, and Intensive Care Unit (ICU)/High Dependency Unit (HDU) rates (England), 2015/16 to 2022/23

Season	Rate per 100,000 population			
	Hospital		ICU/HDU	
	Cumulative	Peak	Cumulative	Peak
2015/16	0.91	0.34	0.14	0.36
2016/17	0.88	0.26	0.07	0.2
2017/2018	83.13	9.4	0.22	0.58
2018/2019	51.06	6.87	0.21 [mean weekly]	0.57
2019/2020	47.22	7.50	0.12 [mean weekly]	0.45
2020/2021	0.30	N/A	N/A[1]	N/A
2021/2022	9.03	N/A	N/A[2]	0.05
2022/2023	87.25	16.65	N/A[3]	0.65

[1] ICU/HDU admission rates for confirmed influenza remained below the baseline threshold level (0.11 per 100,000 trust catchment population) for the duration of the 2020/2021 influenza season

[2] ICU or HDU admission rates for confirmed influenza remained below the baseline threshold level (0.11 per 100,000 trust catchment population) for the duration of the 2021/2022 influenza season [3] ICU or HDU admission rates for confirmed influenza crossed the threshold for the medium impact range (0.18 per 100,000 trust catchment population)

Drug Resistant Influenza

Emergence of virus isolates resistant to influenza antiviral agents continues to be a global public health concern. Two classes of antiviral medications with activity against influenza viruses have been developed. The adamantane derivatives amantadine and rimantadine, available from the 1960s and 1990s respectively, act by binding to and blocking the M2 ion channel of influenza A, preventing virus replication in infected cells [Bright, 2006]. The first neuraminidase inhibitors (NAIs) zanamivir and oseltamivir were introduced in the late 1990s and early 2000s, respectively and in 2018 peramivir was granted a marketing authorisation in the EU for the treatment of uncomplicated influenza. The NAIs act by inhibiting viral cleavage of sialic acid from the cell surface glycoconjugates of infected cells, preventing viral spread in the respiratory tract.

A single point mutation in the coding sequence for the amino acid at a number of positions of the M2 protein is sufficient to confer resistance to adamantanes, which does not hinder replication or transmission of resistant viruses. Whilst global A/H3N2 influenza adamantane resistance was low (<1%) in the 1990s [Dong, 2015], reported levels increased rapidly in the early 2000s, with almost all isolates resistant by 2006 [Nelson, 2009]. Reports of similar levels of resistance in other influenza A strains at this time prompted changes in treatment guidelines, with the use of use of adamantanes no longer recommended [Dong, 2015].

The A(H1N1) flu viruses carrying the H275Y mutation have proven resistant against oseltamivir [Takashita, 2015] while retaining sensitivity to zanamivir. Widespread high-level

resistance to oseltamivir was first detected among the seasonal influenza A(H1N1) virus in the 2007/08 season, with 16% A(H1N1) resistance observed in Europe. In the subsequent 2008-2009 season, almost all A(H1N1) viruses circulating in the Northern Hemisphere, including those in Europe, were resistant to oseltamivir [Lackenby, 2008], meaning that zanamivir was the only approved drug at the time that retained activity against this circulating seasonal H1N1 strain. The H275Y mutation that gives rise to oseltamivir resistance also confers resistance to peramivir.

The 2007/08/2008/09 seasonal A(H1N1) virus was subsequently displaced by influenza A(H1N1) pdm09 virus resulting in the 2009 global influenza pandemic. Resistance to oseltamivir in this virus strain during the pandemic was only detected in a limited number of community cases [WHO, 2009; CDC, 2009; ECDC, 2011], and the global incidence of oseltamivir-resistant virus has remained low, ranging from 0.8%-1.6% in 2011-2014 based on data from the WHO [Lackenby, 2011; Takashita, 2015]. Based on reports in The European Surveillance System (TESSy) for the influenza season of 2010/11, 117/2,562 (4.6%) A(H1N1)pdm09 viruses screened for resistance to NAIs were found to be resistant. All viruses tested remained sensitive to zanamivir (ECDC, 2011). Furthermore, European Centre for Disease Prevention and Control (ECDC) surveillance reports for 2014/15 and 2015/16 did not identify any zanamivir resistant viruses, with <1% of viruses tested exhibiting reduced inhibition by zanamivir in subsequent influenza seasons through 2022/2023 [ECDC, 2024a].

Complicated influenza patients who are refractory to or intolerant of other approved anti- influenza therapies

Oseltamivir is only available as oral formulations and there are some patients with complicated influenza, particularly those in the ICU population, that require an IV formulation. Furthermore, an IV formulation of zanamivir may benefit complicated influenza patients who cannot use the inhaled formulation (e.g., those who cannot actively inhale, those with chronic lung disease, children aged less than 5 years and intubated patients). The reported characteristics of patients with complicated influenza vary depending on season, country, setting and, in the case of pandemic influenza, whether all patients were described or just those from earlier waves of infection (Table 5). Nevertheless, approximately a third of patients admitted with complicated influenza have ongoing respiratory disease (median 33%; range 23- 59%), with asthma and chronic obstructive pulmonary disorder predominating. Critical care therapy is indicated in complicated influenza patients with clinical signs of organ or system failure, such as respiratory failure, haemodynamic instability or altered consciousness [Alvarez-Lerma, 2017]. Approximately a fifth of complicated influenza patients (median 23%; range 9-71%) are directly or subsequently admitted to critical care settings during their hospital stay. Mechanical ventilation occurs primarily in the critical care setting, and, although the reported frequency in individual studies is generally lower than the reported frequency of critical care, the overall levels are similar (median 22%; range 20-64%). There was unprecedented use of ECMO (extracorporeal membrane oxygenation) observed during the influenza A(H1N1) 2009 pandemic.

Table 5 Reported frequency of concurrent respiratory disease, critical care admission and mechanical ventilation among hospitalised influenza patients.

Year/ Season	Strain	Setting	Patients	Reference
2009/10	H1N1v*	National, Germany	71.2% critical care 64.4% MV	[Adlhoch, 2012]
2009/10	H1N1v*	National, Spain	33.2% respiratory disease 9.7%% critical care	[Delgado-Rodriguez, 2013]
2009/10	H1N1v*	Cataluña , Spain	37.9% critical care	[Godoy, 2011]
2009/10	H1N1v*	Andalusia, Spain	22.6% respiratory disease 9.0% critical care	[Mayoral, 2009]
2009/10	H1N1v*	National, UK	33.2% respiratory disease 12.4% critical care	[Myles, 2012]
2009/10	H1N1v*	National, England	21.6% critical care	[Mytton, 2012]
2009/10	H1N1v*	Lyon, France	59.4% respiratory disease 23.2% critical care 20.3% MV	[Payet, 2013]
2010/11	H1N1v*	National, Spain	26.3% respiratory disease 24.6% critical care	[Delgado-Rodriguez, 2013]
2010/11	H1N1v*	National, England	25.0% critical care	[Mytton, 2012]
2012/13	H1N1v*	Freiburg, Germany	26% critical care 23% MV	[Huzly, 2015]
2013/14	H3N2	Freiburg, Germany	20% critical care 20% MV	[Huzly, 2015]

*influenza A(H1N1)pdm09; MV, mechanical ventilation

PREVALENCE

Prevalence is not a relevant measure for an infectious disease such as influenza where acute disease episodes occur.

SI.1.1 Demographics of the population in the authorized indication and risk factors for the disease:

Uncomplicated influenza

Considerable variation in the incidence of seasonal influenza can be observed, depending on circulating strains, vaccine coverage/effectiveness, patient susceptibility and health-seeking practices. The highest primary care consultation rates for influenza-like illness occur in young children compared to adults and in women compared to men [Dijkstra, 2009; Cromer, 2014, Hardelid, 2015], although the predominant circulating strain can strongly dictate the age pattern of infection (Table 6, [RKI, 2024, RKI 2024a]). Increasing deprivation is associated with higher primary care influenza consultation rates [Hardelid, 2015] but the role of ethnicity in this setting is inadequately described.

Table 6 Age-specific seasonal influenza rate, in relation to predominant strain(s), Germany, 2016/17 to 2022/23

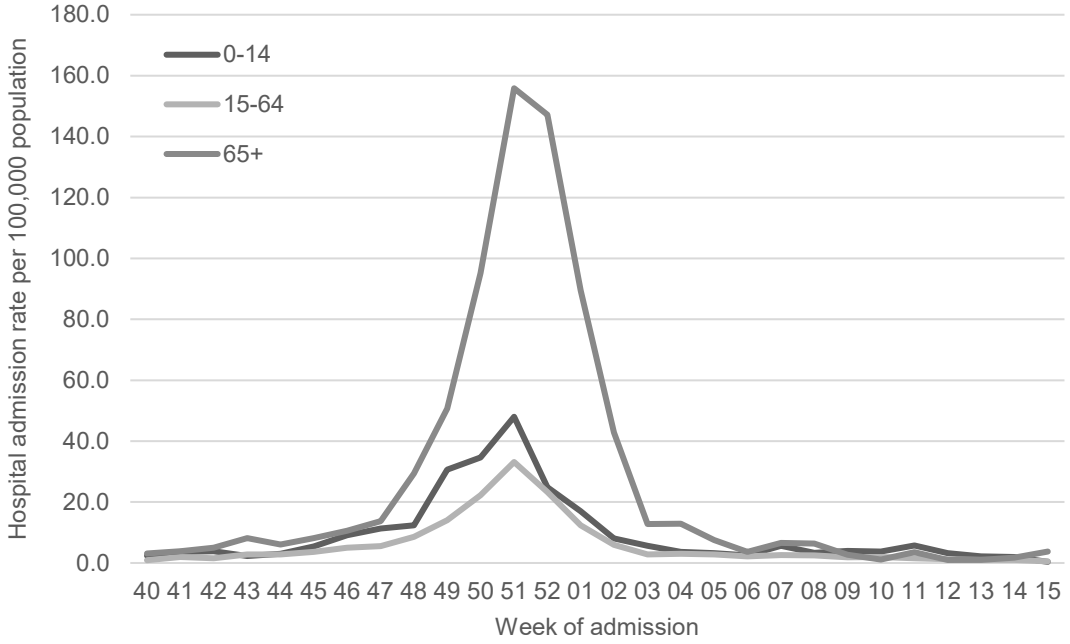
Age	Rate per 100,000 population in each season				
	2016/17	2017/18	2018/19	2019/20	2022/23
0-14	197.86	551.09	421.6	573.78	888.68
15-19	130.74	277.31	176.82	283.68	564.58
20-24	63.43	153.45	140.85	177.22	348.91
25-29	72.44	164.86	173.93	210.11	330.02
30-39	79.25	269.24	213.23	242.42	384.79
40-49	86.47	313.9	181.25	171.68	235.97
50-59	121.84	395.72	230.45	189.26	208.95
60-69	96.65	289.16	179.62	134.9	204.04
70-79	126.71	286.28	187.63	122.53	204.77
80+	220.33	397.9	309.68	201.64	443.88
Predominant strain:	A(H3N2)	A(H1N1)[2] B/Yam	A(H1N1)[2] A(H3N2)	A(H1N1)[2] A(H3N2)	A(H3N2)

[1], starting with calendar week 27; [2]A(H1N1)pdm09

Complicated influenza

Reported rates of hospitalisation for complicated influenza consistently highlight an increased risk in infants and young children [Montes, 2005; Nicholson, 2006; Ajayi-Obe, 2008; Silvennoinen, 2011], with admission rates in children aged 0-4 years more than twice that observed in adults aged 25-64 years. Among children, hospital admission increases with decreasing age, with admission rates four times higher in children aged <12 months compared to older children [Nicholson, 2006] and between eight and twelve times higher in children aged <6 months [Montes, 2005; Silvennoinen, 2011].The age-specific incidence of hospitalised flu among European adults is less clear. Prior to the 2009 pandemic, seasonal flu admission rates were higher in the elderly compared with younger adults [Widgren, 2010; Jacks, 2012; Cromer, 2014]. Whilst this trend continued in some countries during the 2009 pandemic [Widgren, 2010; Jacks, 2012], decreasing rates with increasing age were reported elsewhere [Campbell, 2011; Ortqvist, 2011], possibly reflecting low infection incidence in older people probably due to pre-existing immunity. Age-specific data for influenza-related hospital admissions for the 2022/2023 season follows the expected trend (Figure 1, [UKHSA, 2023]).

Figure 1 Rate of influenza hospitalisations by age group in England, surveillance week 40 2022 to week 15 2023



SI.1.2 The main existing treatment options

When the H3N2 seasonal and 2009 H1N1 pandemic influenza viruses were shown to be 100% resistant to adamantanes, health agencies recommended using NAIs (oseltamivir and zanamivir) for treatment of influenza [Fiore, 2011]. The available data for peramivir do not support a conclusion that peramivir is effective in patients with complicated influenza. Baloxavir marboxil, a cap-dependent endonuclease inhibitor, was approved in the European Union in 2020 for the treatment of uncomplicated influenza in patients aged 12 years and above [EMA, 2023].

NAIs are most effective if administered within 48 hours of onset of symptoms in uncomplicated influenza illness and, based on real world observational data, may be effective if administered beyond 48 hours from symptom onset in complicated/severe influenza [Adisasmito, 2010; Louie, 2012; Muthuri, 2013; Muthuri, 2014]. Treatment with NAIs was associated with reduced mortality risk by 19%-87% in hospitalised influenza patients [Hanshaoworakul, 2009; Lee, 2010; Muthuri, 2014], while treatment within 2 days of symptom onset was associated with a reduced mortality risk by 52% compared with later treatment [Muthuri, 2014].

WHO guidelines, which originate from the time of the 2009 pandemic, recommended that patients with severe or progressive clinical illness be treated with oral oseltamivir and that treatment should be initiated as soon as possible [WHO, 2010]. In situations where (1) oseltamivir is not available or not possible to use, or (2) if the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir, patients who have severe or progressive clinical illness should be treated with zanamivir, where feasible, with intravenous administration as the preferred route of administration despite its investigational status at the time the guidance was issued. More recent European and US guidelines also recommend treatment of all patients hospitalised with complicated influenza as soon as possible and include zanamivir aqueous solution administered by nebulisation or intravenously as second line therapy [UKHSA, 2021; CDC, 2024]. According to these guidelines, zanamivir aqueous solution can be considered for the treatment of complicated influenza where poor clinical response is observed or where subtype testing

confirms a strain with potential oseltamivir resistance, e.g. A(H1N1) or for patients unable to take oral medication.

Whilst recent circulating seasonal strains have largely retained sensitivity to NAIs, the threat of emerging resistance remains. Many patients identified with oseltamivir resistant virus are also immunocompromised and thus at high risk of severe illness and complications of influenza, as well as a longer duration of severe illness due to a reduced ability to clear virus. Published reports from the IV zanamivir Compassionate Use Program (CUP) highlight a number of these cases for whom IV zanamivir was requested due to the current lack of adequate treatment options; many of these patients had suspected or documented oseltamivir-resistant influenza.

These reports highlight a critical unmet medical need for IV formulations of effective anti- influenza agents to treat complicated influenza infection in patients with limited therapeutic options.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Acute influenza infection is an illness of the upper respiratory tract. Typically, after an incubation period of several days, there is a rapid onset of fever and symptoms that include chills, myalgia, headache, malaise, anorexia, sore throat and cough. Symptoms generally improve within about a week, but cough and malaise may persist. Fever of 38-40°C, may last for up to 5 days. Subjects are generally confined to bed while fever is present and are incapable of routine activity at work school or in the home.

Complicated influenza predominantly involves localisation of virus to the lower respiratory tract. Complications include viral pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS) and multi-system organ failure, as well as exacerbation of underlying lung diseases (e.g. asthma and chronic obstructive pulmonary disease) involving the bronchi and small airways. Patients of all ages are at risk for complicated influenza illness. Risk factors include pregnancy, age over 65 years, infants and young children, chronic medical diseases such as diabetes mellitus, kidney, liver, neurological, lung and cardiac disease, compromised immune system and morbid obesity.

Patients with chronic respiratory diseases, and asthma in particular, are more likely to experience complicated influenza infection. Chronic respiratory diseases were the most common reported underlying condition in both adults and children hospitalised for pandemic influenza reported in metropolitan France between July and November 2009 [Fuhrman, 201]. Asthma was also the most commonly reported underlying condition among children (16%) and adults (31%) infected with pandemic influenza in the United Kingdom between May and September 2009 and was the most frequent risk factor associated with hospitalisation in the first wave of the pandemic in Ireland [Nguyen-Van-Tam, 2010; Cullen, 2009]. Other studies, however, note that the prevalence of underlying conditions increases with age in both adults and children hospitalised for complicated influenza [Pebody, 2011; Silvennoinen, 2011].

It has been consistently shown that influenza epidemics are associated with large numbers of deaths amongst elderly patients, particularly those with certain underlying medical conditions. Mortality is highest amongst elderly patients in residential units. Also of note, in some epidemics, mortality in those aged <19 years has accounted for up to 12% of deaths, and only about half of these are associated with a high-risk condition [Teo, 2005]. Seventy-five percent of influenza deaths and 90% of excess influenza winter deaths occur in those aged 65 years and over. Mortality in the elderly is 20 to 30-fold higher in the presence of underlying medical conditions [Stephenson, 2002]

SI.1.4 Important co-morbidities

Co-morbidity	Incidence and prevalence
Asthma	Underlying asthma or bronchospastic disease could be worsened by influenza, which is known to be associated with increased airways hyper-responsiveness. During the 2009/2010 H1N1 influenza pandemic, 25% of patients with severe acute respiratory infection (SARI) in the 18-44 age group in the European region had asthma. In the 2-17 years age group, 10% of patients had asthma (ECDC website).
Chronic lung disease	Chronic lung disease was identified as one of the main underlying conditions leading to SARI during the 2009/2010 H1N1 pandemic. Among SARI patients in the European region, 16% of patients in the 2-17 years age group had chronic lung disease (ECDC website)
Pregnancy	Similar to asthma and chronic lung disease, pregnancy has been associated with the development of influenza and was one of the main underlying conditions leading to SARI during the 2009/2010 H1N1 pandemic. Among SARI patients in the European region, 40% of patients in the 18-44 years age group were pregnant (ECDC website).
Obesity	First recognized as a factor associated with severe infection in the 2009/2010 H1N1 pandemic, obesity and severe obesity has been associated with higher hospitalisation rates [Morgan, 2010] prolonged ICU admission [Diaz, 2011] and increased risk of death [Morgan, 2010].
Immunosuppression	Immunosuppression is associated with more severe influenza and has been linked with reduced vaccine efficacy [Ortqvist, 2011] and the development of oseltamivir resistance [ECDC, 2010]. Reported prevalence during the 2009/2010 pandemic: • 0.1% in the community (Germany [Gilsdorf, 2009]) • 9.0% and 9.4% among hospitalised patients in France [Fuhrman, 2010] and Ireland [Cullen, 2009] respectively • 20% and 22% of fatal cases in the UK [Pebody, 2010] and France [Fuhrman, 2010] respectively. Whilst reported prevalence in the Netherlands at this time was lower (2.5% hospitalised; 2.0% ICU; 4.3% deaths) this still exceeded levels (0.2%) in the general population [van 't Klooster, 2010]

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE:

Table 7 Key Safety findings (from non-clinical studies)

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat-dose toxicity: Zanamivir was well tolerated by all species, at all doses, and by all routes of exposure.	No clinically relevant findings were identified.
Nephrotoxicity: Continuous, IV infusion of zanamivir for 14 days at doses ≥864 mg/kg/day resulted in a dose-related, reversible vacuolation of the proximal convoluted tubules in the renal cortex in male and female rats. The no observed adverse effect level (NOAEL) for this finding in rats was 432 mg/kg/day. There were no test article-related effects in dogs administered zanamivir at doses up to 90 mg/kg/day. Systemic exposure at the NOAEL of 432 mg/kg/day was approximately 3.9-fold the clinical proposed commercial IV dose of zanamivir (600mg BID). Following repeated IV administration for 14 days, no adverse systemic toxicity was observed in the rat or dog at systemic exposures approximately 3.9-fold (rat) and 1.6-fold (dog) the clinical exposure at the proposed commercial IV dose of zanamivir (600mg BID).	No clinically relevant findings were identified; the renal tubular vacuolation was consistent with hydropic swelling similar to that reported as a transient adaptive response following infusion of hypertonic solutions.
Hepatotoxicity: No relevant findings.	No clinically relevant findings were identified.
Genotoxicity: Zanamivir was not genotoxic in a battery of in vitro and in vivo genetic toxicity tests	Zanamivir does not represent a genotoxic hazard to humans.
Reproductive/Developmental toxicity: No drug-related malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits or their fetuses following intravenous administration of zanamivir at dose up to 90 mg/kg/day. Following subcutaneous administration of zanamivir in an additional rat embryofetal development study, there was an increase in the incidence rates of a variety of minor skeletal and	No clinically relevant findings were identified.

Key Safety findings (from non-clinical studies)	Relevance to human usage
visceral alterations and variants in the exposed offspring at the highest dose 80 mg/kg, three times daily (TID; 240 mg/kg/day total daily dose). Based on AUC measurements, the 80 mg/kg TID dose (240 mg/kg/day) produced an exposure approximately 3 times greater than the human exposure at the proposed commercial IV dose of zanamivir (600 mg BID). However, in most instances, the individual incidence rate of each skeletal alteration or variant remained within the background rates of the historical occurrence in the strain studied.	
In the peri- and post-natal developmental study conducted in rats, there was no clinically meaningful impairment of development of offspring.	No clinically relevant findings were identified.
Intravenous doses of up to 90mg/kg/day zanamivir produced no effect on fertility and reproductive function of the treated or subsequent generation in male and female rats.	No clinically relevant findings were identified.
Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs and there was no evidence of teratogenicity. In rats, zanamivir has been shown to be excreted in low amounts into milk.	There is no information on placental transfer of zanamivir or excretion of zanamivir into milk in humans. As experience is limited, the use of zanamivir in pregnancy and breastfeeding mothers should be considered only if the possible benefit to the mother is thought to outweigh any possible risk to the fetus or child, respectively.
Juvenile rats aged 2 days at start of treatment were dosed SC with zanamivir at 1, 9 or 90 mg/kg/day for 41 days (from post-natal day 2 to post-natal day 42. There were no adverse treatment-related effects on juvenile rats related to zanamivir administration. Systemic exposure (Cmax) at the NOAEL, was approximately 6-fold those in humans at the proposed commercial adult dose of 600 mg twice daily.	No clinically relevant findings were identified.
Carcinogenicity: There were no tumorigenic findings considered to be related to zanamivir administration in the 2-year carcinogenicity studies in rats and mice.	Zanamivir does not represent a carcinogenic risk in humans.
General Safety pharmacology: In safety pharmacology studies, zanamivir administered at doses up to 100 mg/kg intravenously in rats and dogs did not produce any overt pharmacodynamic effects on respiratory rate,	No clinically relevant findings were identified from general safety pharmacology studies.

Key Safety findings (from non-clinical studies)	Relevance to human usage
body temperature, the gastrointestinal tract, or on the central or autonomic nervous systems. In the cardiovascular system, some minor effects were observed including transient, non-dose-related, increases in arterial blood pressure (lasting less than 4 minutes) at IV doses of 10 mg/kg and 30 mg/kg in the cat. However, in the conscious dog, zanamivir at IV doses up to 30 mg/kg had no effect on arterial blood pressure, heart rate, electrocardiogram rhythm or PR or QT intervals or on respiratory rate.	
Other toxicity-related information or data:	
Zanamivir has low protein binding and is eliminated by passive renal filtration of unchanged drug.	All patients should have renal function assessed and the dose of zanamivir solution for infusion adjusted accordingly.
In vitro studies indicate that zanamivir is not an inhibitor or substrate of BCRP, P-glycoprotein, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2 transporters, nor was it an inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4, and nor was it an inducer of CYP1A2, 2B6 or 3A4 at clinically relevant concentrations.	Zanamivir has low potential for drug-drug interactions.
Zanamivir was non-irritant to the eyes and skin of rabbits and was devoid of skin sensitisation and antigenic potential in guinea pigs.	No clinically relevant findings were identified.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The inhaled dry powder formulation of zanamivir (RELENZA) has a well characterised safety profile supported by 14,000 adults and paediatric subjects who participated in treatment and prophylaxis studies. As inhaled zanamivir is a well-established product with over 25 years post-marketing experience, clinical trial exposure data is only provided for IV zanamivir.

Table 8 Duration of exposure to IV zanamivir

Cumulative (person time)		
	Subjects	**Person time (days)**
Completed Studies		
Single Dose	120	221
≤5 days	241	855
> 5 – 10 days	432	2744
>10 days	63	698
Total	844	4518
Ongoing Study		
Duration of Exposure for Repeat Dose Studies		
≤5 days	2	0.35
> 5 – 10 days	0	NA
>10 days	0	NA
Total	2	0.35

Single dose studies include: C92-083 (N=8), NAIB1003 (N=17), NAIB1008 (N=22), NAI108127 (N=16), NAI114346 (N=39), and NAI115070 (N=18); Repeat dose studies include: NAIB1009 (N=12), NAIA1010 (N=8), NAI106784 (N=39), NAI117104 (N=24), NAI113678 (N=201), NAI114373 (N=410), NAI115070 (N=12) and NAI115215 (N=21).

Ongoing clinical trials: Clinical pharmacology study 200925

[1] Duration of Exposure is calculated using calendar days vs. 10 -day course of treatment. Three subjects received more than a 10-day course of treatment; all other subjects with >10 days had a 10-day course of treatment but over 11 calendar days. This includes subjects who received zanamivir as a rescue medication.

[2] The number of patients for repeat dose studies includes the subjects who switched to open label zanamivir in study NAI114373. Eleven subjects received Oseltamivir in the treatment blind phase and then switched to open label zanamivir.

Table 9 Age group and gender (IV zanamivir)

Age group	Subjects		Person time (days)	
	M	F	M	F
Completed Studies				
Infants and toddlers				
6 months to less than 1 year	6	1	39	6
1 year to less than 2 years	7	4	31	27
Children				
2 years to 5 years	8	4	43	24
6 years to 12 years	18	9	82	71
Adolescents				
13 years to 17 years	13	6	69	30
Adults				
18 years to 64 years	357	214	1794	1216
Elderly people				
65-74 years	58	36	334	184
75-84 years	48	28	276	139
85 + years	10	17	51	102
Total	525	319	2719	1799
Ongoing Study				
Less than 6 months	2	0	0.35	NA
Greater than or equal to 6 months	0	0	NA	NA
Total	2	0	0.35	NA

Studies included in this analysis are C92-083, NAIB1003, NAIB1008, NAIB1009, NAIA1010, NAI108127,NAI114346, NAI115070, NAI106784, NAI117104, NAI113678, NAI114373 and NAI115215.
Ongoing clinical trials: Clinical pharmacology study 200925

Table 10 Dose (IV zanamivir)

Dose of exposure	Patients	Person time (days)
Completed Studies		
Zanamivir <300mg/day	78	100
Zanamivir 300mg/day	24	108
Zanamivir 400mg/day	10	10
Zanamivir 500mg/day	9	18
Zanamivir 600mg/day	267	1334
Zanamivir 1200mg/day	543	2948
Total	844	4518
Ongoing Study		
IV Zanamivir 10 mg/mL	2	0.35
Total	2	0.35

Subjects in crossovers studies are counted in each of the treatment groups they were exposed to but are only counted once in the total number of subjects. Studies included in this analysis are C92-083, NAIB1003, NAIB1008, NAIB1009, NAIA1010, NAI108127, NAI114346, NAI115070, NAI106784, NAI117104, NAI113678, NAI114373, and NAI115215. The number of patients for repeat dose studies includes the subjects who switched to open label zanamivir in study NAI114373. Eleven subjects received Oseltamivir in the treatment blind phase and then switched to o pen label zanamivir.
Ongoing clinical trials: Clinical pharmacology study 200925

Table 11 Ethnic origin

Ethnic origin	Patients	Person time (days)
Completed Studies		
White - White/Caucasian/European Heritage	589	3074
Asian - East Asian Heritage	60	427
African American/African Heritage	58	243
Asian - Japanese Heritage	42	235
Asian - Central/South Asian Heritage	27	172
Asian - South East Asian Heritage	21	122
White - Arabic/North African Heritage	15	101
American Indian or Alaskan Native	11	53
Mixed Race	4	20
Native Hawaiian or other Pacific Islander	4	15
Missing	13	56
Total	844	4518
Ongoing Study		
White - White/Caucasian/European Heritage	2	0.35
Total	2	0.35

Note: Studies included in this analysis are C92-083, NAIB1003, NAIB1008, NAIB1009, NAIA1010, NAI108127, NAI114346, NAI115070, NAI106784, NAI117104, NAI113678, NAI114373, and NAI115215
Ongoing clinical trials: Clinical pharmacology study 200925

In addition, an IV zanamivir GSK-supported drug-interaction study (NAI112977) was also conducted between July and October 2009. This was an open, randomised, multiple dose, drug interaction study of IV zanamivir and oral oseltamivir, in 16 healthy Thai adults (14 males and two females). All 16 subjects received four treatment regimens, including IV zanamivir 600mg twice daily, for three days and continuous infusion 50mg/h for three days.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

The information below is for IV zanamivir.

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

Table 12 Exclusion criteria

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
Phase III - NAI114373 protocol: Female subjects who were pregnant or were breastfeeding.	Included as GSK standard safety exclusion criteria. [While excluded in Phase III, pregnant women were not excluded in Phase II study NAI113678].	Yes See section SVII.1.2	
Phase III - NAI114373 protocol: Underlying chronic liver disease with evidence of severe liver impairment. Liver toxicity criteria based on local laboratory results obtained within 24 hours of Baseline: Alanine transaminase (ALT) or aspartate transaminase (AST) ≥3x Upper Limit of Normal (ULN) and bilirubin ≥2xULN ALT ≥5xULN	Included as GSK standard safety exclusion criterion as subjects with significant underlying liver disease/condition could either affect the safety of the patient participating in the studies or could affect the efficacy or safety analyses if the underlying disease/condition became exacerbated during the study.	No	The pharmacokinetic profile of IV zanamivir is not likely to be different in patients with hepatic impairment as zanamivir is not metabolised or modified by the liver and is excreted by passive renal filtration of unchanged drug. No safety signal was observed in the Phase III NAI114373 study population which allowed inclusion of subjects with mild hepatic impairment. Overall, in clinical trials, 33 subjects (with an overall exposure of 207 patient days) had underlying hepatic impairment. In the CUP, an optional case report form to collect safety and clinical follow-up data, was returned for 783 patients. Of these, 22 patients had underlying cirrhosisor chronic liver disease.

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
Original NAI114373 protocol: History of severe cardiac disease or clinically significant arrhythmia (either on ECG or by history) which, in the opinion of the Investigator, will interfere with the safety of the individual subject. QT criteria at Baseline as defined below: QTcB or QTcF >500 msec If a subject has bundle branch block, then criteria is QTcB or QTcF >530 msec. Amended to: History of severe cardiac disease or clinically significant arrhythmia (either on ECG or by history) which, in the opinion of the Investigator, will interfere with the safety of the individual subject [QTc critieria removed].	Standard safety exclusion criteria in patients/subjects with significant underlying cardiac disease/condition that could affect the safety of the patient participating in the studies. A formal thorough QTc study, to assess the effect of IV zanamivir on QTc in human subjects, had not been conducted prior to the start of enrolment into Phase II and III studies.	No	A formal thorough QTc study (NAI114346) demonstrated that neither a single therapeutic (600 mg) dose nor a single supratherapeutic (1200 mg) dose of IV zanamivir had any effect on cardiac repolarisation as measured by QTc interval duration. QTc exclusion and withdrawal criteria were removed from Phase II and III studies following availability of favourable results from thorough QTc study NAI114346. Cardiac events have not been demonstrated to be a risk with intravenous zanamivir.
NAI114373 protocol: Subjects who require Extra Corporeal Membrane Oxygenation (ECMO) at Baseline. (enrolled subjects who subsequently required ECMO could continue in the study)	Subjects were excluded due to the potential variability in PK for patients on ECMO and thus difficultly in determining the appropriate dose recommendation. However, if subjects subsequently required ECMO during the study, they were allowed to continue or were withdrawn at the	No	In Phase III studyNAI114373, no subjects in the influenza positive population and in the 600mg IV zanamivir group required ECMO at any point in the study. Subjects requiring ECMO were not excluded from the Phase II study NAI113678: four adult subjects and four paediatric/adolescents received ECMO either at Baseline or during this study. Although data are limited, PK parameters for subjects who received CRRT and/or ECMO appeared similar to

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
	discretion of the investigator.		those for subjects not receiving these interventions.
NAI114373 protocol: Subjects with creatinine clearance ≤ 10 mL/min who are not being treated with continuous renal replacement therapy (CRRT). Subjects who require routine/intermittent hemodialysis or continuous peritoneal dialysis at Baseline. Defined CRRT modalities allowed.	Subjects meeting either of these criteria were excluded due to the inability to provide appropriate dosing for oseltamivir as the blinded comparator in the study.	No	Subjects with severe renal impairment or those requiring haemodialysis were not excluded from the Phase II study NAI113678. Zanamivir is eliminated as unchanged drug by renal excretion and clearance is highly correlated with renal function. There is no preclinical evidence of active transport. Renal elimination governs zanamivir PK and total clearance is highly correlated with renal function (i.e., CLcr). Study NAI108127, a PK study evaluating single 100mg IV zanamivir doses in subjects with impaired renal function and subjects with normal renal function provides data to support recommendations for dose adjustments in renally impaired patients that deliver systemic zanamivir exposure comparable to that from the dose selected (600mg) for subjects without renal impairment. Dose adjustments for renal impairment were implemented in Phase II and III studies for adult and paediatric patients and are clearly communicated in the SmPC.

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

Given the small number of clinical trials and the duration of follow-up on patients who participated in the studies, the clinical development programme for IV zanamivir is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

A broad population of hospitalised subjects (aged ≥6 months to ≥ 65years) was studied in the IV zanamivir clinical development program, and included individuals with a variety of co- morbidities, thus generally reflecting the patient population likely to require IV zanamivir for the treatment of complicated influenza in the indicated patient population.

Table 13 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure	
	Total number of subjects	Duration (person time - days)
Pregnant women	3	22
Breastfeeding women	0	0
Patients with relevant comorbidities:		
• Patients with hepatic impairment	33	207
• Patients with renal impairment	65	257
• Patients with cardiovascular impairment	436	2593
• Immunocompromised patients	120	721
Population with relevant different ethnic origin	There are no known relevant ethnic origin differences	
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms	
Other	No other relevant special populations identified	

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

IV Zanamivir

The algorithm used to derive post-approval exposure data from IQVIA is based on available sales volume data, where 30 vials equates to 1 patient treatment course (600 mg, twice daily, for 5 days).

Inhalation Zanamivir

The algorithm used to derive post-approval exposure data from IQVIA is based on available sales volume data concerning numbers of units sold, where 1 unit is assumed to equate to 1 Diskhaler with 5 days' supply of zanamivir.

SV.1.2 Exposure

IV zanamivir

The cumulative post-marketing experience for IV zanamivir up to 31 December 2023 is estimated to be 749 treatment courses.

Inhaled zanamivir

The cumulative post-marketing experience for inhaled zanamivir up to 31 December 2023 is estimated to be 46.7 million treatment courses.

There have been no subgroups where patterns of reports with inhaled zanamivir indicate a safety signal. Although neuropsychiatric events are more common in children with influenza, a causal association to zanamivir has not been established (see Part II, section SVII.3.1 'Important potential risk 1').

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The potential for drug dependence and abuse of zanamivir has not been evaluated. However, the potential for misuse for illegal purposes with zanamivir is unlikely given that there is no evidence that zanamivir crosses the blood brain barrier or is centrally active; zanamivir has little or no potential for abuse and has no known properties that would suggest possible development of dependence.

To date, there is no indication that inhaled and IV zanamivir has been abused.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

This EU-RMP is an update to the currently approved EU-RMP version 03. This update not only includes information on the approved inhaled medicinal product and but also contains information on IV zanamivir which is the subject of a MAA in the European Union. Therefore, the safety concerns for IV zanamivir are presented here in section SVII.1 ('Identification of safety concerns in the initial RMP') and changes to the safety concerns for inhaled zanamivir are presented in section SVII.2 ('New safety concerns and re-classification with a submission of an updated RMP').

During the IV zanamivir clinical development programme, the reported adverse events were characteristic features of severe influenza and a hospitalised patient population. Assessment of causality in this population was confounded by severe influenza and often severe or chronic underlying disease, and multiple concomitant medications. However, certain safety concerns have been considered as important potential risks for IV zanamivir based on experience with the inhaled formulation of the active substance. These safety concerns are considered 'potential' rather than 'identified' based on the strength of the evidence currently available for IV zanamivir. In addition, use in pregnancy and lactation are added to the list of safety concerns for IV zanamivir as missing information categories.

Table 14 Summary of Safety concerns for IV zanamivir

Risk Category	Safety concern
Important Potential Risks	Cardiac reactions (cardiacarrhythmias) Severe cutaneous reactions Hepatic failure Neuropsychiatric events Antiviral resistance/lack of efficacy
Missing Information	Use in Pregnancy Lactation

There have been no newly identified safety concerns since the last module submitted.

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

The following events are not considered important for inclusion in the list of safety concerns; oropharyngeal oedema, facial oedema, anaphylactic/anaphylactoid reactions, diarrhoea, alanine transaminase increased, aspartate transaminase increased, alkaline phosphatase increased, hepatocellular injury, rash, urticaria.

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):

None.

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:

None.

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):

Oropharyngeal oedema, facial oedema, anaphylactic/anaphylactoid reactions.

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

Diarrhoea, alanine transaminase increased, aspartate transaminase increased, alkaline phosphatase increased, hepatocellular injury, rash and urticaria.

Other reasons for considering the risks not important:

None.

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

Important Potential Risk 1: Cardiac reactions (cardiac arrhythmias)

In April 2018, the CHMP issued the Day 120 List of Questions during the MAA submission for Dectova (IV zanamivir) [EMA/CHMP/250018/2018]. This included a request to discuss whether cardiac arrhythmias should be included in the safety specifications of the EU-RMP for Dectova.

In order to conduct a comprehensive review of the events of arrhythmias in patients receiving IV zanamivir, a search of the GSK global safety database (ARGUS) using the Broad Standardised MedDRA Query (SMQ) for cardiac arrhythmias was conducted in April 2018. Fifty-five cases were retrieved, the majority from the CUP, six cases from the pivota1 Phase III study, 10 cases from the Phase II study. All of the cases occurred in patients who were seriously unwell. Many described patients who were on mechanical ventilation and in 35 cases the outcome was fatal. The available evidence does not suggest that any particular age group is at additional risk. The events appear to be associated predominantly with severe influenza infection although this reflects the nature of the patients in the CUP.

Three serious treatment-related cases of cardiac arrhythmia were reported in Phase II and Phase III trials. One was a patient in the IV zanamivir 300 mg arm of pivotal study NAI114373 (one event of cardiac arrest, possibly related as considered by the investigator). Two patients in the adult cohort of open-label Phase II study NAI113678 (3 events; Torsades de Pointes, ventricular

arrhythmia and ventricular tachycardia. In the first case, the investigator considered that there was no reasonable possibility that the cardiac arrest was caused by zanamivir but that there was a reasonable possibility that the ventricular arrhythmia and Torsades de Pointes, which occurred 16 days after completing therapy, may have been caused by zanamivir.

However, the investigator also considered that the events were also possibly due to the concomitant medication, suxamethonium and haloperidol, and the Torsades de Pointes to be complications of influenza. In the second case the investigator considered that there was a reasonable possibility that the ventricular tachycardia may have been caused by zanamivir as no other cause was identified.

GSK's response to the Day 120 List of Questions concluded that the detailed review of individual cases does not support a causal relationship between IV zanamivir and cardiac arrhythmias in general, or between IV zanamivir and any particular type of cardiac arrhythmia. The reported cases are heavily confounded by the severely-ill status of patients receiving compassionate use treatment. Although "cardiac arrhythmias" is an adverse drug reaction (ADR) stated in the summary of product characteristics (SmPC) for oseltamivir (Tamiflu SmPC), the scientific evidence for this is not apparent in the published literature, and there is currently insufficient evidence to suggest a class effect.

Further to GSK's response to the Day 120 List of Questions, in the Day 180 List of Outstanding Issues received from the CHMP in October 2018, the CHMP requested that cardiac reactions (cardiac arrhythmias) is added to the list of safety concerns as an important potential risk for Dectova. The CHMP acknowledged that the evidence for including any recommendation in SmPC section 4.4 or inclusion of cardiac arrhythmias in SmPC 4.8 is not considered justified for the moment. However, the patient population to be treated with IV zanamivir includes patients with complicated influenza with risk factors for cardiac reactions. Therefore, it is of interest to monitor this safety concern and address this separately in future PSURs.

Therefore, cardiac reactions (cardiac arrhythmias) will be monitored in the EU-RMP as an important potential risk for IV zanamivir. No additional risk minimisation measures or additional pharmacovigilance (PV) activities are proposed for cardiac reactions. However, GSK proposes to monitor these events using routine PV activities to inform the risk-benefit balance of IV zanamivir.

Important Potential Risk 2: Severe cutaneous reactions

Severe cutaneous reactions are recognised as very rare adverse drug reactions for inhaled zanamivir and are considered unlikely to be formulation-specific.
The GSK global safety database (ARGUS) was searched using the Narrow Standardised MedDRA Query (SMQ) 'severe cutaneous reactions' in patients receiving IV zanamivir and identified four cases with seven events. In most of the cases, the events were non-serious. Of two serious adverse event (SAE) cases in the CUP, one was a poorly documented case of Stevens-Johnson syndrome. Although the prescribing physician's causality assessment was unknown, given that SJS is an adverse reaction for the inhaled powder formulation of zanamivir, GSK considered that there was a reasonable possibility that the event may have been caused by IV zanamivir, although there was minimal information to judge causality. The other case was an unrelated case of 'dermatitis bullous (superior gluteal cleft)' which resolved, although the patient later died from worsening of acute respiratory distress syndrome. There was one SAE of toxic skin eruption, considered unrelated by the investigator, in the open-label Phase II study

NAI113678. The event occurred 11 days after completion of IV zanamivir treatment and resolved after one day. The patient was a 65-year old with HIV who was receiving intensive care and multiple concurrent medications. The treating physician considered the event may be due to concomitant co-trimoxazole and valganciclovir.

A review of cases identified from a search of the global safety database using the Broad SMQ 'Hypersensitivity' supports the addition of 'rash' and 'urticaria' to the SmPC as adverse reactions in section 4.8. However, the current evidence does not support the addition of the specific term 'severe cutaneous reactions'. Nevertheless, given that severe cutaneous reactions of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are included in the SmPC for inhaled zanamivir, a warning in section 4.4 of the IV zanamivir SmPC is included and the PTs erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are included in section 4.8 with a frequency of 'not known'. These events will be monitored in the EU-RMP as an important potential risk for IV zanamivir. No additional risk minimisation measures or additional PV activities are proposed for the important potential risk of severe cutaneous reactions. However, GSK proposes to monitor these events using routine PV activities to inform the risk-benefit balance of IV zanamivir.

Important Potential Risk 3: Hepatic Failure

Raised transaminases in both seasonal influenza and 2009 pandemic H1N1 patients have been documented (Papic 2012). This retrospective study reviewed hospital records of patients with laboratory-confirmed influenza, 86 with seasonal influenza and 97 with 2009 pandemic H1N1. Liver function tests prior to NAI treatment demonstrated a pattern of mild hepatocellular injury, which may have its aetiology in hypoxaemia, cytokine release or viral specific CD8+ T-lymphocytes. AST was above upper limit of the normal range in 36% of pandemic patients and 18.6% of seasonal flu patients and ALT was elevated in 26% and 7.4%, respectively. Lactase dehydrogenase and GGT were also frequently elevated in both groups.

Nevertheless, hepatic events of increased transaminases and hepatocellular injury are proposed for inclusion in section 4.8 of the SmPC based on data from the clinical trials. The incidence of these events in study NAI114373 was similar in the three arms (zanamivir 300mg, 600 mg and oseltamivir), suggesting a similar safety profile for zanamivir and oseltamivir. The inclusion of the terms increased transaminases (specifically increased ALT, AST and ALP) and hepatocellular injury would be broadly consistent with the SmPC for oseltamivir, which lists elevated liver enzymes, hepatitis, fulminant hepatitis and hepatic failure.

However, the evidence from clinical trials does not support the addition of hepatic failure to section 4.8 of the SmPC for IV zanamivir. Five serious adverse events of hepatic failure, considered by the treating physician as attributable to zanamivir, were reported in the CUP. Assessment of causality of these cases is confounded by the patients' underlying medical conditions, severe disease, including multi-organ failure, and concomitant medications.

Therefore, GSK does not propose adding hepatic failure as an adverse reaction to section 4.8 of the SmPC. However, hepatic failure is considered an important potential risk and will be closely monitored by routine PV to collect more data (see section SVII.3.1).

Important Potential Risk 4: Neuropsychiatric Events

Reports of neuropsychiatric events, including convulsions, depressed level of consciousness, abnormal behaviour, hallucinations and delirium, with the inhaled formulation of zanamivir have been reviewed and none of the safety information received to date has suggested a causal

relationship between neuropsychiatric events and zanamivir. However, the possibility of neuropsychiatric events occurring is communicated to patients and prescribers via warnings in the SmPC and Patient Information Leaflet (PIL), and neuropsychiatric events remain as an important potential risk for inhaled zanamivir in the EU-RMP.

Based on experience with inhaled zanamivir, neuropsychiatric events of convulsions, depressed level of consciousness, abnormal behaviour, hallucinations and delirium are considered an important potential risk for IV zanamivir.

Important Potential Risk 5: Antiviral Resistance/Lack of Efficacy

To date, selection of drug resistant variants is rare following exposure to IV zanamivir. However, emergence of virus isolates resistant to zanamivir continues to be a potential threat.

Missing Information 1 – Use In Pregnancy

Pregnant women are a group at risk of increased influenza-related morbidity and mortality. As such, pregnant women are at higher risk of complicated influenza and hospitalization, and exposure to IV zanamivir is likely to occur.

Non-clinical data

Non-clinical reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs. There is no information on placental transfer in humans.

Clinical development programme (IV zanamivir)

Zanamivir exposure in pregnant women was very limited in the clinical development programme for IV zanamivir. Pregnant or breastfeeding women were excluded from the Phase III clinical trial. However, although not excluded from the Phase II study NAI113678, only three pregnant women were enrolled. One subject, in the third trimester, gave birth by Caesarean section at 29 week's gestation age, to a normal female infant (approximately 3 months after study participation). The second subject, exposed in the third trimester of pregnancy, gave birth by normal vaginal delivery at 29 weeks' gestation (approximately 3 weeks after completion of treatment), to a live female infant with no congenital abnormalities. The third subject, exposed in the second trimester (at 25 week's gestation), gave birth by Caesarean section at 39 weeks, to a live male infant with no apparent congenital abnormalities gestation.

Spontaneous adverse reactions – intravenous zanamivir

A cumulative review of pregnancy and lactation cases involving zanamivir in the GSK Safety database was undertaken in July 2022. Of the 1198 eligible cases reported, 16 involved IV zanamivir with seven of the 16 cases reporting fatal maternal outcomes. Fifteen cases were reported by Healthcare Professionals and one case was reported by a Regulatory Authority.

In the seven fatal cases, one live birth was reported, one emergency caesarean with no foetal outcome, and five cases reported no foetal outcome. All the cases involved pregnant women hospitalised with influenza, six in their third trimester and one at 24 weeks of pregnancy. The type of events reported in these cases were as expected in serious cases of influenza and include events such as cardiopulmonary arrest, acute respiratory distress syndrome and respiratory failure.

Of the nine non-fatal cases, four were serious and in two (reporting maternal events of abnormal liver function tests and worsening thrombocytopenia respectively) the investigator considered there was reasonable possibility the events were related to IV zanamivir. In both cases the events resolved, and the pregnancy was ongoing at time of last follow up.

A third serious case involved a patient in her first trimester of pregnancy with events of leukocytosis, increased platelet count, increased blood alkaline phosphatase and increased gamma glutamyl transferase. The patient underwent a therapeutic abortion to improve her clinical situation. The outcome was unknown. The events were assessed by the reporting physician as unrelated to zanamivir.

The final serious case reported events of respiratory failure and hypoxia in a patient at 29 weeks of pregnancy who received inhaled zanamivir, followed by a single dose of IV zanamivir after admission to ICU. Within hours of receiving IV zanamivir her condition improved, and she was prescribed inhaled zanamivir again. No assessment of causality was provided by the reporting physician. A live birth with no anomalies was reported at 39 weeks of pregnancy.

All five of the non-serious cases reported a live birth. No congenital anomalies have been reported in live births following administration of IV zanamivir during pregnancy.

Literature reports

A large European study of population-based registers from Denmark, Norway, Sweden and one region of France (EFEMERIS database) reported on outcomes of nearly 6,000 infants exposed to NAIs in pregnancy during the 2009-2010 H1N1 pandemic. Data from prescription registers, capturing NAI exposure during pregnancy, were linked to birth registers capturing information on birth outcomes (Graner, 2017). Seventy-four percent of NAI exposures were to oseltamivir and 26% to zanamivir. Exposure to NAIs in utero was not associated with increased risks of any of the following neonatal outcomes: low birth weight, low Apgar score, preterm birth, small for gestational age birth, still birth, neonatal mortality, and neonatal morbidity. The authors concluded that this study found no increased risks of adverse neonatal outcomes or congenital malformations associated with exposure to neuraminidase inhibitors during embryo- foetal life, however zanamivir specific data were not reported.

Dunstan, 2014 identified exposures to zanamivir during pregnancies that were voluntarily reported to the UK Teratology Information Service during the 2009-2010 H1N1 pandemic. Exposed pregnancies were followed to assess the risk of adverse pregnancy outcomes. Outcomes for 180 zanamivir exposures and 575 prospectively enrolled pregnancies exposed to non-teratogenic medications were compared over the same period. In live-born infants, no significant differences were observed in overall risk of major malformation [adjusted odds ratios (aOR) 0.37 [95% confidence interval (CI) 0.02–2.7], preterm delivery [aOR 0.95 (95% CI 0.45, 1.89)], or low birthweight [aOR 0.94 (95% CI 0.25, 2.90] following exposure to zanamivir at any gestational age. No congenital anomalies were reported among 37 first trimester exposures to zanamivir.

A prospective case series of NAI-exposed pregnancies included 50 pregnant women exposed to zanamivir (15 in the first trimester) and 619 pregnant women exposed to oseltamivir (159 during the first trimester) (Saito, 2013). Treatment was either therapeutic or prophylactic following exposure to influenza. The rates of miscarriage and preterm deliveries did not appear to be increased in either treatment group nor when comparing those who were infected or uninfected with influenza. The rates of foetal adverse events including convulsion and other transient abnormalities such as transient tachypnea, respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, infection with fever, hypothyroidism, and vomiting did not appear to be increased compared to previously reported data. No congenital malformations were observed in 15 infants exposed to zanamivir during the first trimester and 35 infants exposed to zanamivir during the second and third trimesters.

A GSK sponsored a non-interventional, retrospective, primary care-based cohort study of inhaled zanamivir exposure in pregnant women was also completed during the 2009- 2010 H1N1 pandemic (Walker, 2014). Electronic medical record data were used to identify 144 women who were prescribed inhaled zanamivir during pregnancy and 144 age and date-matched healthy pregnancy comparators. The two groups were assessed for pre-treatment characteristics, treatment-emergent diagnoses in the mother, pregnancy outcomes and congenital malformations diagnosed in the offspring within 28 days of birth. There was no evidence of a difference between inhaled zanamivir and healthy comparator group in the risk of any treatment-emergent diagnosis. The number of major congenital anomalies reported among comparators (14/144) was higher than among the women exposed to zanamivir (4/144). The greatest imbalance was in cardiac defects (zanamivir, n=1, comparator n=6). Prematurity was reported in two infants exposed to zanamivir and was not reported in the comparator group. Low birth weight was reported in one infant in both groups. There was no indication of increased risk of adverse pregnancy events in the mother or the infant from inhaled zanamivir exposure based on descriptive analyses from this small series. Prescribing of zanamivir could be for therapeutic or prophylactic reasons, but numbers were too small for stratification.

Several studies have demonstrated that in women with influenza, prompt antiviral use reduces maternal mortality and adverse pregnancy outcomes (Knight, 2011; Donaldson, 2009) although a small study using health registry data demonstrated an increased risk of late transient hypoglycemia in infants exposed in utero, but no other adverse increased risks of adverse birth outcomes among infants exposed to NAIs compared to unexposed infants (Svensson, 2011).

Compassionate Use Programme (IV zanamivir)

In the CUP, up to 31 January 2020, 60 patients have received zanamivir aqueous solution either during pregnancy or shortly postpartum/post-foetal death. However, detailed information is not available on all subjects due to the nature of this program, and limited information is available on the GSK safety database for 16 pregnant patients as described above.

Overall, the available information from clinical trials and the CUP, on pregnancy outcomes, are too limited to make an assessment of the safety of IV zanamivir in pregnancy.

A post-authorisation safety study (Pregnancy Registry Study 208140) was initiated to evaluate pregnancy outcomes, among hospitalised pregnant women who receive IV zanamivir at any time during pregnancy, including: 1) maternal outcome or maternal death, 2) pregnancy outcomes including spontaneous losses, induced abortions, stillbirths and live births and 3) birth outcomes including birth weight, small for gestational age, prematurity, congenital malformations and neonatal death. Infants will be followed after birth to allow outcome ascertainment.

This pregnancy registry study was primarily descriptive and designed to detect potential safety signals. Despite GSK's best efforts to enrol patients, no patients were recruited into the study and in June 2023 GSK requested approval from EMA to close the study as part of the Pregnancy Registry Annual Update submission (EMEA/H/C/004102/MEA/003.2). EMA endorsed closure of this study on 14 September 2023. GSK continue to monitor clinical safety in pregnancy with routine pharmacovigilance measures.

Missing Information 2 – Lactation (Exposure During Breast-Feeding)

There is insufficient knowledge to determine if the safety profile of IV zanamivir in breast-feeding mothers differs from that already characterised. In rats, zanamivir has been shown to be secreted into milk. However, there is no information on secretion into breast milk in humans.

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

This EU-RMP is an update to the currently approved EU-RMP version 07 to remove the information of Pregnancy registry (PASS) study as per the outcome of EMEA/H/C/004102/MEA/003.2.

New safety concerns

There are no new safety concerns for inhaled and IV zanamivir.

Re-classification of safety concerns

None.

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 Potential Risk 1	**Cardiac reactions (cardiac arrhythmias) - [IV zanamivir]**
Potential Mechanism	A potential mechanism for cardiac arrhythmia with IV zanamivir is not known given that no clinically relevant findings were identified from non-clinical studies and a formal thorough QTc study (NAI114346) in 40 healthy volunteers demonstrated that neither a single therapeutic (600 mg) dose nor a single supratherapeutic (1200 mg) dose of IV zanamivir had any effect on cardiac repolarisation as measured by QTc interval duration.
Evidence source and strength of evidence	The evidence for a causal association between IV zanamivir and cardiac arrhythmias is limited. There are in total 55 cases of arrhythmias reported, most reported in the CUP, but also three serious treatment-related cases in Phase II and Phase III trials. “Cardiac arrhythmias” is an adverse drug reaction stated in the SmPC for oseltamivir (Tamiflu SmPC). However, the scientific evidence for this is not apparent in the published literature, and there is insufficient evidence to suggest a class effect.
Characterisation of the risk	A search of the GSK global safety database for cases of cardiac arrhythmia retrieved 55 cases which described use of the IV formulation of zanamivir. Most cases were from the CUP, six cases were from the pivotal Phase III study NAI114373, 10 were from the open-label Phase II study NAI113678 and one came from CUP retrospective chart review (NAI115008). The available evidence does not suggest that any particular age group is at additional risk. All of the cases occurred in patients who were seriously unwell. Many described patients who were on mechanical ventilation and in 35 cases the outcome was fatal.

	Detailed review of individual cases does not support a causal relationship between IV zanamivir and cardiac arrhythmias in general, or between IV zanamivir and any particular type of cardiac arrhythmia. <u>IV zanamivir clinical trials</u> Three cases of serious treatment-related events in the cardiac disorders SOC were reported in the clinical development programme. In NAI114373, one patient in the IV zanamivir 300 mg arm had one event of cardiac arrest, possibly related as considered by the investigator. In NAI113678, two patients in the adult cohort had 3 events: Torsades de Pointes; ventricular arrhythmia; and ventricular tachycardia. In the first case, the investigator considered that there was no reasonable possibility that a cardiac arrest was caused by zanamivir but that there was a reasonable possibility that events of ventricular arrhythmia and Torsades de Pointes, which occurred 16 days after completing therapy, may have been caused by zanamivir. However, the investigator also considered that the events were also possibly due to the concomitant medication, suxamethonium and haloperidol, and the Torsades de Pointes to be complications of influenza. In the second case the investigator considered that there was a reasonable possibility that the ventricular tachycardia may have been caused by zanamivir as no other cause was identified. <u>Inhaled zanamivir</u> There is extensive post-marketing experience with inhaled zanamivir (Relenza) from more than 25 years of real-life clinical use with global post-marketing experience of >46.7 million treatment courses (as of 31 Dec 2023). The global product information does not contain any cardiac adverse reactions although it is acknowledged that the inhaled delivery route requires a much smaller dose and limited systemic exposure compared to the intravenous route.
Risk Groups or risk factors	Persons of any age with chronic cardiac disease (e.g. congestive cardiac failure) are at risk of complicated influenza which can result in exacerbation of their underlying illness (WHO, 2010). Cardiovascular involvement in influenza can occur through direct effects of the virus on the myocardium presenting as myocarditis, with associated electrocardiogram (ECG) changes, or through exacerbation of existing cardiovascular disease. Cardiovascular mortality is increased during influenza seasons in those patients with pre-existing coronary artery disease, and myocardial infarction rates have also been shown to increase during epidemics (Estabragh, 2013).
Preventability	The patient population to be treated with IV zanamivir are patients with complicated influenza with risk factors for cardiac reactions (cardiac arrhythmias). This population will be monitored for cardiac arrhythmias in the clinical situation as part of routine clinical care for severely ill patients requiring intensive care.

Impact on benefit-risk balance of the product	As evidence of causal association between IV zanamivir and cardiac reactions is limited, and a warning in section 4.4 of the SmPC is not considered justified, the benefit-risk balance is considered favourable for IV zanamivir.
Public health impact	Cardiac arrhythmias were observed in the CUP and IV zanamivir clinical development programme. However, detailed review of individual cases does not support a causal relationship between IV zanamivir and cardiac arrhythmias in general, or between IV zanamivir and any particular type of cardiac arrhythmia. Therefore, the potential public health impact is judged to be very low.

Important Potential Risk 2	**Severe cutaneous reactions (IV zanamivir)**
Potential Mechanism	The pathogenesis of severe skin reactions is not entirely understood, though several studies have supported involvement of the immune system in SJS and TEN. A widespread apoptotic process is thought to be the cause of the acute necrosis of keratinocytes seen in TEN. Genetic factors may also play a role in the development of SJS and TEN. Patients with SJS/TEN appear to have a strong genetic predisposition towards particular drugs, which also varies by ethnicity [Mockenhaupt, 2009].
Evidence source and strength of evidence	Post-marketing experience with inhaled zanamivir; IV zanamivir clinical trials; zanamivir aqueous solution CUP. Occasional reports of severe skin reactions associated with inhaled zanamivir inhalation powder were received during the post-marketing period. These included SJS, TEN, erythema multiforme (EM), bullous dermatitis and toxic skin eruption. The issue was originally reviewed by GSK in April 2009 and concluded that there was insufficient evidence to support a causal relationship with inhaled zanamivir. A further review was conducted in July 2009 following the receipt of follow-up information on a patient who had developed biopsy-confirmed SJS after exposure to inhaled zanamivir with a corresponding positive drug lymphocyte stimulation test. Based on this second review, it was considered that there was a reasonable possibility of a causal relationship with inhaled zanamivir. No cases of SJS, TEN or EM were reported in the IV zanamivir clinical trials. One case of SJS was reported in the CUP but it was insufficiently well documented to allow an assessment of the causal relationship to zanamivir.
Characterisation of the risk	<u>IV zanamivir clinical trials</u> Across the IV zanamivir clinical development programme and CUP, four cases containing seven PTs included in the Narrow SMQ 'severe cutaneous reactions'were reported. In most cases, the events were non-serious. One SAE of toxic skin eruption was reported in the open-label Phase II study NAI113678, in a 65-year-old HIV patient receiving intensive care. The event occurred

	11 days after the end of zanamivir treatment and resolved after one day. The treating physician did not consider the event to be related to IV zanamivir and instead considered that it may be due to concomitant co-trimoxazole and valganciclovir. One non-serious AE of drug eruption (drug rash) was reported in another adult in the Phase II study NAI113678. The event, which was unresolved, was considered unrelated to zanamivir by the investigator. In the paediatric/adolescent cohort of this study, one subject had non-serious AEs of drug eruption on Day 6, and blister (on toes, chest and hands) post-treatment. Both events resolved and both were considered unrelated to zanamivir. The blisters were reported as complications of influenza by the investigator. Another subject experienced mild skin exfoliation of the hands, post-treatment which resolved and was considered unrelated to zanamivir by the investigator. In the Phase III study NAI114373, one post-treatment non-serious AE of blister (blisters on right upper extremity), considered by the investigator as treatment- related, was reported in the 300mg IV zanamivir arm. The blisters did not resolve and the patient died due to acute kidney injury, methicillin resistant staphylococcus aureus, pneumonia, respiratory failure, septic shock and tachycardia. Two non-serious AEs of skin exfoliation were reported; one occurred post-treatment in the 600mg IV zanamivir arm and resolved. The other was in the oseltamivir arm and occurred during treatment and was unresolved. Both were considered unrelated to study treatment by the investigator. <u>CUP</u> In the CUP, two SAE reports of severe cutaneous reactions were reported. One was a poorly documented case of SJS, which was unresolved at the time of reporting. Although a prescribing physician assessment of causality was unknown, GSK considered the event was possibly related to IV zanamivir, given that the event is an adverse drug reaction for the inhaled powder formulation of zanamivir, although there was minimal information to judge causality. The second report was a case of dermatitis bullous (superior gluteal cleft) which occurred 9 days after completion of zanamivir treatment and resolved, although the patient later died from worsening of acute respiratory distress syndrome. The event was considered by the treating physician as unrelated to zanamivir.
Risk Groups or risk factors	Severe cutaneous reactions are known to be triggered by infectious agents (Mockenhaupt, 2009). Therefore, patients with influenza or concomitant infections may be at greater risk.

Preventability	These events cannot be prevented or predicted. However, as severe cutaneous reactions of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are included in the SmPC for Relenza (inhaled zanamivir), the possibility of serious hypersensitivity reactions including erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome is included in the Dectova SmPC section 4.4 and erythema multiforme, SJS and toxic epidermal necrolysis are included in section 4.8 as adverse drug reactions with a frequency of 'not known' as requested by the CHMP.
Impact on benefit-risk balance of the product	The frequency of these events with IV zanamivir is rare. Severe cutaneous reactions are well known to healthcare professionals who apply appropriate intervention treatment/mechanisms as part of clinical practice. Therefore, the benefit-risk balance is considered favourable for IV zanamivir.
Public health impact	Severe cutaneous reactions were rare in the IV zanamivir clinical development programme and CUP. Therefore, the potential public health impact is judged to be very low.

Important Potential Risk 3	**Hepatic failure (IV zanamivir)**
Potential Mechanism	A potential mechanism remains unclear, given that non-clinical data shows that there is little or no hepatic involvement in the metabolism or excretion of zanamivir, and very low direct cytotoxicity. As doubts remain over a causal association, severe influenza itself, concurrent illnesses, and concomitant medications must be considered as equally possible causes of the hepatic failure in patients with complicated influenza.
Evidence source and strength of evidence	Hepatic failure cases (N=8) have been reported in the CUP and assessed by the investigator as related to zanamivir. All cases were confounded by concomitant severe illness and concurrent medications. Increased liver function tests were reported in subjects receiving DECTOVA zanamivir across Phase I, II and III studies. Positive causality has not been established between IV zanamivir and hepatic events at this time, with the majority of cases reported to date being confounded by indication, concomitant medications, and/or underlying medical conditions.

Characterisation of the risk	A review of non-clinical data did not show any hepatic findings in preclinical species at exposures in excess of those proposed clinically, no significant hepatic burden, little or no hepatic metabolism or excretion, no metabolic alerts, and very low direct cytotoxicity. No clinically significant liver abnormalities were identified in IV zanamivir healthy volunteer studies. Cases of raised liver function tests were seen in Phase II and Phase III studies in patients receiving IV zanamivir, some of which met the criteria for a SAE and/or the protocol-specified liver chemistry stopping criteria. Amongst the related, serious AEs in the Phase II/III studies, in the "Hepatobiliary Disorders" SOC, two events of hepatocellular injury were reported with zanamivir 600mg IV treatment, both in the adult cohort of NAI113678. There were no such serious events in the paediatric cohort of NAI113678, in the Japanese study NAI115215, nor in the Phase I studies. A small number of hepatic failure cases (N=8) have been reported in the CUP, which were assessed by the investigator as related to zanamivir. Although detailed information is not available on all subjects due to the nature of this programme, all were confounded by the severity of the patients' influenza- related disease, and/or other serious underlying medical conditions, or concurrent medications.
Risk Groups or risk factors	Hepatic events have been primarily associated with the IV formulation, which has high systemic availability relative to inhaled zanamivir. The IV formulationis indicated for critically-ill hospitalised patients with complicated influenza, who may be at greater risk of hepatic events, including hepatic failure, due to serious co-morbidities.
Preventability	The possibility of increased ALT, AST, ALP and hepatocellular injury is stated in the SmPC section 4.8. More severe liver injury will be monitored in the clinical situation as part of routine clinical care for severely ill patients requiring intensive care. A paragraph has been included in the Physicians' Guidance Document to physicians who request IV zanamivir via the CUP to inform them of the potential for hepatic events.
Impact on benefit-risk balance of the product	Causality has not been established between zanamivir and hepatic events. GSK continues to monitor all reports of these events to further characterise gain a clearer understanding the potential risk of hepatic failure.
Public health impact	As the IV formulation is indicated for critically-ill hospitalised patients with complicated influenza, the public health impact is low.

Important Potential Risk 4	**Neuropsychiatric events - particularly in children and adolescents (inhaled zanamivir)** **Neuropsychiatric events (IV zanamivir)** – insufficient data to determine any specific population at risk
Potential Mechanism	Unknown. The pharmacokinetic characteristics of zanamivir make a direct CNS toxicity mechanism for neuropsychiatric events unlikely. Animal models with IV zanamivir demonstrated no exposure in the central nervous system and showed no evidence of any consistent treatment-related clinical signs that indicate an effect of zanamivir on behaviour. Zanamivir inhalation powder is very poorly absorbed and systemic exposure to drug is low. Influenza is known to occasionally occur with neurological involvement including encephalopathy [Studahl, 2003].
Evidence source and strength of evidence	Spontaneous reports with inhaled zanamivir; Literature articles <u>Spontaneous reports with inhaled zanamivir</u> In 2005, GSK became aware of two reports of possible suicides of Japanese teenagers receiving oseltamivir. As a result, a review of all neurological and psychiatric events from inhaled zanamivir clinical studies and spontaneous sources was carried out. In spring 2007, GSK observed an increase in the number of spontaneous neuropsychiatric events with inhaled zanamivir received from Japan, coinciding with a public release of a high-level alert by the Japanese Ministry of Health, Labor and Welfare in March 2007 concerning abnormal/self-harming behaviours observed in Japanese adolescents with influenza who were exposed to oseltamivir. Therefore, in 2007 a further review of clinical and post-marketing reports was conducted: A total of nine SAEs relating to neurological or psychiatric conditions were identified and did not appear to follow any consistent clinical pattern. In all cases, a plausible non- drug aetiology was identified and no SAEs suggested a causal relationship to inhaled zanamivir. This review was submitted to the Reference Member State (MPA – Sweden) and all concerned EU member states in November 2007. This review was updated in 2008 to take account of reports received during the 2007/2008 northern hemisphere flu season, and no new safety concerns were identified. On assessment of PSUR 2012N311341_00 (reporting period 01 February 2011 to 31 January 2012), the Swedish MPA requested a cumulative review of all fatal events in children and adolescents, with a particular focus on those with concomitant neuropsychiatric events, following a report of completed suicide in an 11 year old, and given the large amount of post-marketing use since the previous review. Of 33 pediatric cases with a fatal outcome, 8 cases had a concomitant neuropsychiatric event. Of these 8 cases, 3 cases were spontaneous reports in patients

	who received inhaled zanamivir; 4 cases were seriously ill patients who received IV or nebulized zanamivir solution on a compassionate use basis, and 1 case was in a seriously ill patient in the IV zanamivir Phase 2 clinical trial (NAI113678). In the 3 cases identified with inhaled zanamivir, 1 case had insufficient detail to make an assessment of causality, although a temporal relationship was noted, and in another patient, a confounding underlying condition and the time interval between the neurological event and stopping inhaled zanamivir make causality unlikely. In the case of completed suicide by hanging,the temporal relationship between inhaled zanamivir dosing and the event of suicide means a casual relationship cannot be ruled out. However, the case is confounded by pre-existing attention deficit hyperactivity disorder-like behavior and Asperger's syndrome, with possible social problems, and there is no good evidence that this is a drug-related event. In 2016, GSK identified a small number of inhaled zanamivir cases involving patients who jumped out of windows or similar self-harming acts. Although there appeared to be a temporal relationship between the events and administration of inhaled zanamivir, in most cases the event was accompanied by fever and/or signs of influenza encephalopathy including hallucination, meaningless speech, somnolence, delirium, abnormal behaviour, or the patient had an underlying psychiatric disorder. On review of the data, there is no clear evidence from clinical trials or post marketing surveillance, and no clear pharmacological plausibility (relatively low systemic absorption) to suggest a safety concern related to neuropsychiatric events and fatal outcomes with inhaled zanamivir. The known association of neuropsychiatric events caused by influenza and influenza encephalitis suggests that the reported neuropsychiatric events are unlikely to be related to treatment with inhaled zanamivir. <u>Medical literature</u> Neurological involvement in influenza can be manifested as Reye's syndrome, acute necrotizing encephalopathy, myelitis, Guillain–Barré syndrome, encephalomyelitis and neuritis. Other observed symptoms include confusion, convulsions, and psychosis (Studahl, 2003). The most frequent neurological manifestations of influenza are encephalitis or encephalopathy. In a retrospective cohort study on influenza-related neurological complications (INCs) in 842 children with influenza, conducted in Pennsylvania, USA, over the years 2000-2004, 72 (8.6%) patients developed INCs and of these 10 (13.9%) developed encephalopathy. The majority of other patients with INC presented with seizures (56) (Newland et al., 2007). In a similar study in Taiwan, over a period of 29 months, 11 (12%) of 92 admitted influenza patients presented with INCs. Four of these patients presented with

	seizures and the remaining 7 with encephalopathy (Lin et al., 2006) In Japan, influenza-associated encephalopathy is one of the most frequent manifestations of influenza and the incidence of this complication has been increasing (Studahl, 2003; Sugaya, 2002). The incidence began increasing after the 1994-1995 epidemic. The cases of influenza-associated encephalopathy occur most frequently in children. (Sugaya, 2002; Togashi, 2004). The typical presentation of influenza-associated encephalopathy is rapid onset of high fever, convulsion and rapidly progressive coma (Sugaya, 2002). However, occasionally abnormal behaviour or delirium has been observed among the affected children in Japan (Okumura, 2005). Huang and colleagues (2003), report five children in Taiwan ranging in age from 3 to 6 years old who experienced visual and auditory hallucinations, in addition to displaying unusual behaviour. These were observed to end once the influenza illness resolved and did not reappear after 2 years of follow-up. These children were characterized as having Influenza A-associated CNS dysfunction. The authors conjecture that there is a current bias in reporting severe neurological manifestations of influenza, while mild and transient manifestations maybe more frequent, but under-reported (Huang, 2003). In Japan, Okumura and colleagues (2006) report observing delirious behaviour in 9 patients ranging in age between 4 and 10 years old. Four of these patients had delirious behaviour after the use of oseltamivir, however the authors report no evidence that oseltamivir was the cause of the delirium. The delirious behaviour included meaningless speech, disorientation, “fearful response”, and “running around the room” (Okumura, 2006). A study in Japan compared the incidence rates of abnormal behaviour among influenza patients administered NAIs versus those not administered NAIs using data obtained from the Japanese National Database of Electronic Medical Claims (Nakamura, 2018). The incidence rate of the most severe abnormal behaviour in patients who did not receive a NAI was significantly higher than that of influenza patients who received zanamivir (or laninamivir) in patients aged five to 19 years, suggesting that NAI administration does not increase the risk of abnormal behaviour in influenza patients.
Characterisation of the risk	<u>Inhaled zanamivir clinical trials</u> In 2005, GSK reviewed 26 Phase II and III centrally-sponsored, placebo- controlled and rimantidine-controlled clinical trials (total number of patients = 14,810) in response to two reports of possible suicides of Japanese teenagers receiving oseltamivir. In placebo-controlled trials, a total of 34 patients (0.4%) receiving zanamivir experienced neurological/psychiatric events vs. 27 (0.4%) receiving placebo. The most common types of event occurring

	in zanamivir-treated patients were depressive disorders (0.2%) and mood disorders (0.1%). There was one serious case of attempted suicide two weeks after completing zanamivir treatment, in a bipolar patient who had come off psychotic medications without medical supervision, and one non-serious AE of suicidal ideation, neither of which was assessed by the investigator as related to zanamivir. In rimantidine-controlled trials, neurological/psychiatric events were reported by 8 (2.4%) of patients receiving inhaled zanamivir, 5 (2.0%) receiving rimantidine and one (7.7%) receiving placebo. The most commonly occurring types of event in the zanamivir groups were confusion (1.2%) and depressive disorders (0.9%). One case of suicidal ideation was reported with rimantidine. No cases of suicidal behaviour were reported with zanamivir. <u>Inhaled zanamivir - Post-marketing reporting data</u> On assessment of the periodic safety update report (PSUR) 2012N311341_00 (reporting period 01 Feb 2011 to 31 Jan 2012), the Swedish MPA requested a cumulative review of all fatal events in children and adolescents, with a particular focus on those with concomitant neuropsychiatric events, following a report of completed suicide in an 11-year-old, and given the large amount of post-marketing use since the previous review. Three relevant spontaneous reports concerning inhaled zanamivir were retrieved from the GSK safety database. One case had insufficient detail to make an assessment of causality, although a temporal relationship was noted, and in another patient, a confounding underlying condition and the time interval between the neurological event and stopping inhaled zanamivir make causality unlikely. In the case of completed suicide by hanging, the temporal relationship between inhaled zanamivir dosing and the event of suicide means a causal relationship cannot be ruled out. However, the case is confounded by pre-existing attention deficit hyperactivity disorder-like behaviour and Asperger's syndrome, with possible social problems. GSK is of the opinion that no change to the current wording in the label was considered necessary. This conclusion was endorsed in the Final Assessment Report, in December 2012, by the Swedish MPA who agreed that there are no clear indications that inhaled zanamivir played a causal role in the fatal outcomes of these cases and that no update to the label was required. Subsequent cases received since 2012 have not altered thisconclusion. <u>IV zanamivir clinical trials</u> Based on experience with inhaled zanamivir, neuropsychiatric AEs are considered a potential risk for IV zanamivir. Overall, in the IV zanamivir clinical development programme, no neuropsychiatric safety signals were identified in adults or

paediatric patients. The frequency of neuropsychiatric AEs reported was low with no patterns of events. The neuropsychiatric SAEs that were reported reflected the severely ill influenza patient population. Although clinical trials data do not suggest that the higher systemic dose of IV zanamivir compared with inhaled zanamivir is associated with a higher risk of neuropsychiatric events, such events may be masked in this very sick population who are often unconscious, and mechanically ventilated.

In Phase III study NAI114373, the frequency and nature of neuropsychiatric AEs was similar between the zanamivir and oseltamivir arms. The most common, occurring in more than one patient in any treatment arm, were headache, dizziness, anxiety, insomnia, delirium, depression, mental status changes and hallucination.

Adverse Events - IV zanamivir

Adverse Event	**IV zanamivir 300mg BID (N=201)**	**IV zanamivir 600mg BID (N=209)**	**Oral oseltamivir 75mg BID (N=205)**
Headache	3 (1%)	9 (4%)	7 (3%)
Dizziness	2 (<1%)	3 (1%)	4 (2%)
Anxiety	1 (<1%)	2 (<1%)	6 (3%)
Insomnia	1 (<1%)	2 (<1%)	4 (2%)
Delirium	1 (<1%)	1 (<1%)	4 (2%)
Depression	2 (<1%)	1 (<1%)	3 (1%)
Mental status changes	2 (<1%)	2 (<1%)	0
Hallucination	0	1 (<1%)	2 (<1%)

Neuropsychiatric SAEs were reported in three subjects. Encephalopathy occurred five days after completion of IV zanamivir treatment in a mechanically ventilated 60-year-old in respiratory failure. The event resolved and the patient recovered. A second SAE report of encephalopathy occurred during treatment in a 72-year-old with sepsis and multi-organ failure. The third subject, who was receiving antidepressant medication prior

	to starting zanamivir experienced an SAE of (worsening of) depression 21 days after the last dose of zanamivir, making causality unlikely. In the paediatric/adolescent cohort of NAI113678 (N=71), the frequency of neuropsychiatric events was low with only one event reported in more than one subject; this was mental status changes which was reported in one subject in cohort 3 (2 years to <6 years) and one subject in cohort 5 (≥13 years to <18 years). No neuropsychiatric events were reported in the two youngest cohorts (6 months to <1 year; and 1 year to <2 years). There was one neuropsychiatric SAE of encephalitis with a fatal outcome, in a severely ill 6-year-old with a history of new onset of altered mental status prior to starting zanamivir. In NAI115215, an open-label study of IV zanamivir 600mg twice daily, in Japanese patients (N=21), very few neuropsychiatric AEs were reported. On- treatment events were delirium 1 (5%) in an 85-year-old and insomnia 1 (5%) in an 82-year-old and in the follow-up period neuropsychiatric events of headache 1 (5%) in a 71-year-old and dementia 1 (5%) in a 78-year-old were reported. <u>CUP</u> Reporting of SAEs was mandatory for the CUP. In the GSK safety database, SAEs in the Psychiatric disorders SOC were reported in three patients: these were agitation, delirium, mutism and transient psychosis. SAEs in the Nervous system disorders SOC were reported in 32 patients and were mainly events associated with severe illness, the most common being cerebral haemorrhage/haemorrhage intracranial (n=14). In the CUP, non-serious AEs were reported via a case report form for a proportion of patients and stored in a study database. Of these reports, non-serious neuropsychiatric AEs were reported in a small number of patients. These were headache and seizure in two patients each and single reports of Guillain–Barré, peroneal nerve palsy, agitation, depression and insomnia.
Risk Groups or risk factors	Based on spontaneous reports with inhaled zanamivir, children and adolescents were identified as being at particular risk of neuropsychiatric events, particularly early in the influenza illness, and especially with concurrent pyrexia and/or influenza encephalopathy/encephalitis, or a relevant underlying psychiatric disorder. In contrast, in the hospitalised population, the frequency of neuropsychiatric events in IV zanamivir clinical trials or in the CUP was low, with no pattern relating to age.
Preventability	<u>Inhaled zanamivir</u> The possibility of neuropsychiatric events (such as convulsions, depressed level of consciousness, delirium, hallucination and abnormal behaviour) occurring has been communicated to

	patients and prescribers via warnings and precautions and undesirable effects sections in the SmPC and PIL. Specifically, in the PIL parents are advised to be especially careful to watch out for these symptoms if their child or teenager has influenza. <u>IV zanamivir</u> The possibility of neuropsychiatric events of convulsions, loss of consciousness, delirium, hallucination and abnormal behaviour occurring is communicated to prescribers via warnings and precautions and undesirable effects in the SmPC and PIL.
Impact on benefit-risk balance of the product	Causality has not been established between zanamivir and neuropsychiatric events. GSK continues to monitor all information on neurological and psychiatric events to gain a clearer understanding of any possible relationship with zanamivir therapy. If causality is established at some point during the product lifecycle of inhaled or IV zanamivir, risk minimisation measures will be considered.
Public health impact	GSK has conducted several reviews of neuropsychiatric events in patients treated with inhaled zanamivir. None of the reviews established a causal relationship to inhaled zanamivir, therefore, the potential public health impact is judged to be low.

Important Potential Risk 5	**Antiviral resistance/lack of efficacy (inhaled zanamivir and IV zanamivir)** MedDRA PTs: those indicative of lack of efficacy or a product complaint (e.g. lack of efficacy; treatment failure; drug effect decreased; drug resistance)
Potential Mechanism	Resistance to zanamivir, a NAI, may be caused by mutations to the active site of the neuraminidase enzyme or by changes to amino acids in or near the receptor binding site of haemagglutinin. Only the first mechanism is thought to be of clinical significance (Pizzorno, 2011).
Evidence source and strength of evidence	Post-authorisation inhaled zanamivir epidemiology study (OTH112321); clinical trials with IV zanamivir; case studies in the medical literature for inhaled zanamivir and zanamivir aqueous solution CUP. To date, selection of resistance substitutions is rare and there is no evidence of emergence of clinically relevant resistance.
Characterisation of the risk	<u>Inhaled zanamivir clinical trials</u> During clinical trials with inhaled zanamivir, susceptibility of virus isolates was monitored in vitro and the neuraminidase gene was sequenced to identify for resistance mutations. Resistance to zanamivir was not observed in more than 14,000 subjects who participated in treatment and prophylaxis clinical studies evaluating the inhaled zanamivir formulation.

	A trial of inhaled zanamivir in 279 children over three influenza seasons did not find any clear evidence of treatment-emergent resistance to inhaled zanamivir. However, a virus isolated on Day 7 of treatment contained the N294K NA amino acid substitution that was not present at Day 1 in the same subject. The virus could not be cultured for phenotyping. Although the N294S mutation is a recognised resistance mutation, it is not known if the N294K reduces susceptibility to zanamivir. Insufficient information is available to characterise the risk of emergence of inhaled zanamivir resistance in clinical use. <u>IV zanamivir clinical trials</u> In the IV zanamivir clinical development programme, one resistance substitution was detected in an immunocompromised adult and one in an immunocompetent child in the Phase II study NAI113678; both viruses could not be cultured for phenotype testing and therefore the impact on zanamivir susceptibility remains unknown. The one treatment-emergent NA resistance substitution (E119G/H1N1pdm09) detected in a post-Baseline sample that was not present at Baseline from an immunocompetent paediatric patient, may be the only NA substitution detected in all clinical studies of zanamivir (including for the inhaled product) in an immunocompetent patient. In general, resistant viruses are replication deficient and, in this study the two resistant viruses with E119D and E119G were only present at one post treatment timepoint and were outgrown by wildtype virus at subsequent timepoints. In the Phase III study NAI114373, no treatment-emergent resistance mutations were detected in the 600mg arm. Two H3N2 viruses with N294N/S and T325I substitutions were recovered, on Day 2, from two immunocompetent subjects treated with IV zanamivir 300 mg BD. In a reverse genetics project, the NA substitution N294S was shown not to confer resistance. Substitution T325I could not be cultured, so therefore was unfit and as the substitution was at a position of variability in other subtypes, may confer reduced susceptibility although conclusive data could not be obtained. <u>Medical literature</u> In the literature, there have been eleven reported cases of reduced susceptibility to zanamivir in viruses isolated from immunocompromised individuals. In an immunocompromised patient infected with influenza B virus, a variant virus emerged after two weeks of treatment with a nebulised solution of zanamivir (Gubareva, 1998). Analysis of this variant showed a hemagglutinin substitution (T198I) which resulted in a reduced affinity for human cell receptors, and a substitution in the NA active site (R152K) which reduced the enzyme's activity to zanamivir by 1,000-fold. There have been four cases of A/H1N1 viruses harbouring the I223R mutation isolated from immunocompromised patients exposed to IV zanamivir (van der

	Vries, 2010; Nguyen, 2010) and inhaled zanamivir (Rousset, 2010; Grund, 2015). All of the patients were treated initially with oseltamivir followed by treatment with zanamivir. The I223R mutation was detected during the initial oseltamivir treatment in two of the patients and conferred a shift in susceptibility with oseltamivir and zanamivir of 46- and 10- fold respectively. A sixth case report described influenza A/H3N2 viruses isolated from an immunocompromised patient at different timepoints with different NA mutations, including E119V, Q136K, R292K and a deletion at 245- 248 (Eshaghi 2014). Viruses with the I223R and E119G substitutions could not be cultured so the effect on susceptibility could not be determined. The patient was treated with 75 mg oseltamivir, 150 mg oseltamivir, 5 mg inhaled zanamivir and 600mg IV zanamivir at different times and there did not seem to be any correlation between the presence of specific mutations and the treatment at the time of detection. The E119D and E119G mutations were identified in three immunocompromised subjects during treatment with IV zanamivir in the CUP (L'Huillier 2015; Tamura 2015). Both the E119D and E119G confer high level resistance to zanamivir. In tenth case of an immuncompromised patient, influenza A/H1N1pdm09 virus harboured NA substitutions at H275Y, I223R, and E119G following treatment with oral oseltamivir, inhaled zanamivir and IV zanamivir (Trebbien 2017). The eleventh case detailed the chronic influenza infection of a pediatric patient following a failed hematopoietic bone marrow transplant. The patient had Influenza B virus and was treated initially with oseltamivir which did not clear the infection even though the virus was susceptible to NA inhibitors based on phenotypic evaluation. Zanamivir resistant sequences were detected 17 days after the first Zanamivir treatment with E117A/G/V detected. Multiple rounds of treatment including oseltamivir, nitazoxanide and zanamivir failed to clear the virus and partially resistant strains continued to be observed The patient was transitioned to a nebulised solution of zanamivir, nitazoxanide plus favipiravir (60 mg/kg/day for 1 day; 23 mg/kg/day 3 time daily for 16 days) combination which led to a reduction in viral load but the virus transiently rebounded with fully resistant virus (E117A/G). A subsequent virus rebound led to a treatment of zanamivir, oseltamivir plus favipiravir which ultimately cleared the virus. However, no susceptibility data was included so difficult to understand the relevance (Lumby CK 2020) Abed, et al.1 reported the development of multi-drug resistance to NA inhibitors, in an immunocompromized patient, during treatment with oseltamivir followed by IV zanamivir. This was a fatal case in a 72 year old male with influenza A(H1N1) pmd09 and concurrent medical conditions of acute myeloid leukemia, allogenic stem cell transplantation and graft versus host disease in the intestine. Oseltamivir rapidly induced the NA mutation H275Y and HA gene substitutions S135A and P183S. When therapy was switched to

	IV zanamivir, NA H275Y and 119E/G/D mixed populations were detected. The mutations H275Y-E119G NA variant were dominating with S135A and P183S HA substitutions in the last patient samples. The authors concluded that oseltamivir can rapidly induce H275Y substitutions in A(H1N1)pdm09 viruses and subsequent treatment with IV zanamivir can lead to additional substitutions at codon E119 resulting in multi-drug resistance. The fitness of these viruses could not be assessed as the clinical isolates were not available to the authors. However, the authors noted that in previous 16 clinical cases, A(H1N1)pdm09 isolates containing E11G Tamura, et al.2 and E11D L'Huillier, et al.3 NA substitutions demonstrated a deficient growth in vitro. Also of interest was a case report detailing the chronic influenza infection of a pediatric patient following a failed hematopoietic bone marrow transplant. The patient had Influenza B virus and was treated initially with oseltamivir which did not clear the infection even though the virus was susceptible to NA inhibitors based on phenotypic evaluation. Zanamivir resistant sequences were detected 17 days after the first Zanamivir treatment with E117A/G/V detected. Multiple rounds of treatment including oseltamivir, nitazoxanide and zanamivir failed to clear the virus and partially resistant strains continued to be observed. The patient was transitioned to a nebulised solution of zanamivir, nitazoxanide plus favipiravir (60 mg/kg/day for 1 day; 23 mg/kg/day TID for 16 days) a combination which led to a reduction in viral load but the virus transiently rebounded with fully resistant virus (E117A/G). A subsequent virus rebound led to a treatment of zanamivir, oseltamivir plus favipiravir which ultimately cleared the virus.No susceptibility data was included so difficult to understand the relevance.4 Also of interest was a case report detailing the chronic influenza infection of a pediatric patient following a failed hematopoietic bone marrow transplant. The patient had Influenza B virus and was treated initially with oseltamivir which did not clear the infection even though the virus was susceptible to NA inhibitors based on phenotypic evaluation. Zanamivir resistant sequences were detected 17 days after the first Zanamivir treatment with E117A/G/V detected. Multiple rounds of treatment including oseltamivir, nitazoxanide and zanamivir failed to clear the virus and partially resistant strains continued to be observed. The patient was transitioned to a nebulised solution of zanamivir, nitazoxanide plus favipiravir (60 mg/kg/day for 1 day; 23 mg/kg/day TID for 16 days) a combination which led to a reduction in viral load but the virus transiently rebounded with fully resistant virus (E117A/G). A subsequent virus rebound led to a treatment of zanamivir, oseltamivir plus favipiravir which ultimately cleared the virus. No susceptibility data was included so difficult to understand the relevance.4 This information does not significantly change the evaluation of the Important Potential Risk of antiviral resistance.

	An article of interest is the study by Wang-Jairaj, et al.5 which described the Global CUP for IV zanamivir.5 This program was put in place in 2009 – alongside the clinical development program for IV zanamivir and in response to the influenza A/H1N1pmd09 global pandemic – and was terminated in 2019 upon the marketing authorization for IV zanamivir in Europe. It facilitated the use of IV or nebulized zanamivir in patients seriously ill with influenza infection for whom approved anti-influenza drugs were not effective or feasible, with a target of drug delivery to hospitals within 24 hours of initial contact. Data were captured via the master summary tracking sheet for initial requests, through a voluntary CRF or via the GSK safety database. Adverse Events meeting the definition of a SAE in patients who received ≥1 dose of zanamivir from the time of the first dose until 14 days after treatment completion were required to be reported; any SAEs reported after this time were included in the GSK safety data set. A total of 4033 requests for zanamivir treatment were received by 6 May 2019, with most requests from Europe (75.7%) or North America (17.7%). The mean (standard deviation) age was 47.3 (0.32) years and 41% were female. Drug administration was almost exclusively IV (≥95%). Among the 819 patients in the CRF with outcome data 39.1% had not recovered or their condition was not resolved, 32.6% had recovered or their condition had resolved and 28.2% had died. Overall, 466 patients reported ≥1 SAE to the GSK Safety Database, with a total of 839 SAEs recorded; 374 (80%) of these patients had a fatal outcome. The overall SAE profile of IV zanamivir was similar to that reported in the clinical development program. The authors concluded that the CUP accomplished its goal of providing IV zanamivir seriously ill patients with influenza infection globally, many of whom had no alternative treatment options. The safety profile for zanamivir in the CUP was consistent with previous reports, and no new safety concerns were identified.Limitations included the non-clinical conditions under which the study was undertaken and its impact on data quality, a lack of generalisability to patients outside the UK and US and the lack of an active comparator population to fully assess the association between zanamivir and clinical outcomes.
Risk Groups or risk factors	Immunocompromised patients, prophylactic use (inhaled zanamivir reduced dosage for prophylaxis); off-label use.
Preventability	Adherence to the dosing regimen as specified in the SmPC and PIL to minimise the potential for development of viral resistance.
Impact on benefit-risk balance of the product	Resistance to zanamivir during treatment is rare. Widespread resistance to zanamivir when administered as the inhaled product has not been described to date. A small number of resistance substitutions have been identified with IV zanamivir; however, the clinical relevance of these is unknown.

Public health impact	Emergence of virus isolates resistant to influenza antiviral agents continues to be a public health concern. Therefore, neuraminidase susceptibility and consequences of development of drug resistance in influenza viruses continues to be monitored globally. As stated in the Reference Member State Assessment report of June 2007 (EMA/456915/2006), there is no indication that NAI resistance in circulating seasonal influenza viruses is associated with worsened viral virulence, atypical influenza clinical symptoms or enhanced transmissibility. In vitro and pre-clinical data have suggested that NAI mutations are often associated with reduced infectivity, replication and pathogenicity. It is not known whether the degree of compromise may vary by type of mutation. Data have suggested that strains of influenza viruses with reduced susceptibility to NAIs circulate in the community and cause a clinical picture indistinguishable from that of non-resistant strains. These resistant strains appeared to have been transmitted from person to person. Zanamivir is active in vitro against some oseltamivir-resistant strains, as well as variants resistant to M2 inhibitors. Development of resistance to zanamivir has not been identified as a significant risk to date; resistance to inhaled zanamivir during treatment is rare. Compared with oseltamivir, zanamivir more closely mimics the structure of the natural substrate of NA. Thus, many mutations that confer resistance to oseltamivir do not demonstrate cross-resistance to zanamivir, which retains activity against the mostly commonly reported influenza virus mutation (H275Y) [Meijer, 2014]. Resistance to zanamivir was not observed in more than 14,000 subjects who participated in treatment and prophylaxis clinical studies evaluating the inhaled zanamivir formulation. Oseltamivir-resistant seasonal H1N1, containing the H275Y substitution, spread rapidly in 2007 and by 2009 had circulated globally with nearly 100% of seasonal H1N1virus containing this substitution. This strain retained sensitivity to zanamivir, which was the only available treatment option at that time since the strain was also resistant to the adamantanes class of antivirals. The pandemic H1N1 strain, which was the dominant circulating strain throughout the 2009/2010 and 2010/2011 seasons, was sensitive to both oseltamivir and zanamivir, although sporadic cases and clusters of oseltamivir-resistant isolates (mostly H275Y variants) were reported [Englund, 2009; Mai, 2010; Lackenby, 2011; Hurt, 2011; Takashita, 2014]. Subsequent circulating seasonal strains have retained sensitivity to both antiviral drugs. The H275Y substitution is known to confer reduced susceptibility to another NAI, peramivir, but to a lesser extent compared with oseltamivir. The threat of emerging resistance remains.

SVII.3.2 Presentation of the missing information

IV Zanamivir

Missing information 1: Pregnant women (IV zanamivir)

Pregnant women are a group at risk of increased influenza-related morbidity and mortality. As such, pregnant women are at higher risk of complicated influenza and hospitalization, and exposure to IV zanamivir is likely to occur.

Non-clinical data

Non-clinical reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs. There is no information on placental transfer in humans.

Clinical development programme (IV zanamivir)

Zanamivir exposure in pregnant women was very limited in the clinical development programme for IV zanamivir. Pregnant or breastfeeding women were excluded from the Phase III clinical trial. However, although not excluded from the Phase II study NAI113678, only three pregnant women were enrolled. One subject, in the third trimester, gave birth by Caesarean section at 29 week's gestation age, to a normal female infant (approximately 3 months after study participation). The second subject, exposed in the third trimester of pregnancy, gave birth by normal vaginal delivery at 29 weeks' gestation (approximately 3 weeks after completion of treatment), to a live female infant with no congenital abnormalities. The third subject, exposed in the second trimester (at 25 week's gestation), gave birth by Caesarean section at 39 weeks, to a live male infant with no apparent congenital abnormalities gestation.

Spontaneous adverse reactions – intravenous zanamivir

A cumulative review of pregnancy and lactation cases involving zanamivir in the GSK Safety database was undertaken in July 2022. Of the 1198 eligible cases reported, 16 involved IV zanamivir with seven of the 16 cases reporting fatal maternal outcomes. Fifteen cases were reported by Healthcare Professionals and one case was reported by a Regulatory Authority.

In the seven fatal cases, one live birth was reported, one emergency caesarean with no foetal outcome, and five cases reported no foetal outcome. All the cases involved pregnant women hospitalised with influenza, six in their third trimester and one at 24 weeks of pregnancy. The type of events reported in these cases were as expected in serious cases of influenza and include events such as cardiopulmonary arrest, acute respiratory distress syndrome and respiratory failure.

Of the nine non-fatal cases, four were serious and in two (reporting maternal events of abnormal liver function tests and worsening thrombocytopenia respectively) the investigator considered there was reasonable possibility the events were related to IV zanamivir. In both cases the events resolved, and the pregnancy was ongoing at time of last follow up.

A third serious case involved a patient in her first trimester of pregnancy with events of leukocytosis, increased platelet count, increased blood alkaline phosphatase and increased gamma glutamyl transferase. The patient underwent a therapeutic abortion to improve her clinical situation. The outcome was unknown. The events were assessed by the reporting physician as unrelated to zanamivir.

The final serious case reported events of respiratory failure and hypoxia in a patient at 29 weeks of pregnancy who received inhaled zanamivir, followed by a single dose of IV zanamivir after admission to ICU. Within hours of receiving IV zanamivir her condition improved, and she was prescribed inhaled zanamivir again. No assessment of causality was provided by the reporting physician. A live birth with no anomalies was reported at 39 weeks of pregnancy.

All five of the non-serious cases reported a live birth. No congenital anomalies have been reported in live births following administration of IV zanamivir during pregnancy.

Literature reports

A large European study of population-based registers from Denmark, Norway, Sweden and one region of France (EFEMERIS database) reported on outcomes of nearly 6,000 infants exposed to NAIs in pregnancy during the 2009-2010 H1N1 pandemic. Data from prescription registers, capturing NAI exposure during pregnancy, were linked to birth registers capturing information on birth outcomes (Graner, 2017). Seventy-four percent of NAI exposures were to oseltamivir and 26% to zanamivir. Exposure to NAIs in utero was not associated with increased risks of any of the following neonatal outcomes: low birth weight, low Apgar score, preterm birth, small for gestational age birth, still birth, neonatal mortality, and neonatal morbidity. The authors concluded that this study found no increased risks of adverse neonatal outcomes or congenital malformations associated with exposure to neuraminidase inhibitors during embryo- foetal life, however zanamivir specific data were not reported.

Dunstan, 2014 identified exposures to zanamivir during pregnancies that were voluntarily reported to the UK Teratology Information Service during the 2009-2010 H1N1 pandemic. Exposed pregnancies were followed to assess the risk of adverse pregnancy outcomes. Outcomes for 180 zanamivir exposures and 575 prospectively enrolled pregnancies exposed to non-teratogenic medications were compared over the same period. In live-born infants, no significant differences were observed in overall risk of major malformation [adjusted odds ratios (aOR) 0.37 [95% confidence interval (CI) 0.02–2.7], preterm delivery [aOR 0.95 (95% CI 0.45, 1.89)], or low birthweight [aOR 0.94 (95% CI 0.25, 2.90] following exposure to zanamivir at any gestational age. No congenital anomalies were reported among 37 first trimester exposures to zanamivir.

A prospective case series of NAI-exposed pregnancies included 50 pregnant women exposed to zanamivir (15 in the first trimester) and 619 pregnant women exposed to oseltamivir (159 during the first trimester) (Saito, 2013). Treatment was either therapeutic or prophylactic following exposure to influenza. The rates of miscarriage and preterm deliveries did not appear to be increased in either treatment group nor when comparing those who were infected or uninfected with influenza. The rates of foetal adverse events including convulsion and other transient abnormalities such as transient tachypnea, respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, infection with fever, hypothyroidism, and vomiting did not appear to be increased compared to previously reported data. No congenital malformations were observed in 15 infants exposed to zanamivir during the first trimester and 35 infants exposed to zanamivir during the second and third trimesters.

A GSK sponsored a non-interventional, retrospective, primary care-based cohort study of inhaled zanamivir exposure in pregnant women was also completed during the 2009- 2010 H1N1 pandemic (Walker, 2014). Electronic medical record data were used to identify 144 women who were prescribed inhaled zanamivir during pregnancy and 144 age and date-matched healthy pregnancy comparators. The two groups were assessed for pre-treatment characteristics, treatment-emergent diagnoses in the mother, pregnancy outcomes and congenital malformations diagnosed in the offspring within 28 days of birth. There was no evidence of a difference between inhaled zanamivir and healthy comparator group in the risk of any treatment-emergent diagnosis. The number of major congenital anomalies reported among comparators (14/144) was higher than among the women exposed to zanamivir (4/144). The greatest imbalance was in cardiac

defects (zanamivir, n=1, comparator n=6). Prematurity was reported in two infants exposed to zanamivir and was not reported in the comparator group. Low birth weight was reported in one infant in both groups. There was no indication of increased risk of adverse pregnancy events in the mother or the infant from inhaled zanamivir exposure based on descriptive analyses from this small series. Prescribing of zanamivir could be for therapeutic or prophylactic reasons, but numbers were too small for stratification.

Several studies have demonstrated that in women with influenza, prompt antiviral use reduces maternal mortality and adverse pregnancy outcomes (Knight, 2011; Donaldson, 2009) although a small study using health registry data demonstrated an increased risk of late transient hypoglycemia in infants exposed in utero, but no other adverse increased risks of adverse birth outcomes among infants exposed to NAIs compared to unexposed infants (Svensson, 2011).

Compassionate Use Programme (IV zanamivir)

In the CUP, up to 31 January 2020, 60 patients have received zanamivir aqueous solution either during pregnancy or shortly postpartum/post-foetal death. However, detailed information is not available on all subjects due to the nature of this program, and limited information is available on the GSK safety database for 16 pregnant patients as described above.

Overall, the available information from clinical trials and the CUP, on pregnancy outcomes, are too limited to make an assessment of the safety of IV zanamivir in pregnancy.

A post-authorisation safety study (Pregnancy Registry Study 208140) was initiated to evaluate pregnancy outcomes, among hospitalised pregnant women who receive IV zanamivir at any time during pregnancy, including: 1) maternal outcome or maternal death, 2) pregnancy outcomes including spontaneous losses, induced abortions, stillbirths and live births and 3) birth outcomes including birth weight, small for gestational age, prematurity, congenital malformations and neonatal death. Infants will be followed after birth to allow outcome ascertainment.

This pregnancy registry study was primarily descriptive and designed to detect potential safety signals. Despite GSK's best efforts to enrol patients, no patients were recruited into the study and in June 2023 GSK requested approval from EMA to close the study as part of the Pregnancy Registry Annual Update submission (EMEA/H/C/004102/MEA/003.2). EMA endorsed closure of this study on 14 September 2023. GSK continue to monitor clinical safety in pregnancy with routine pharmacovigilance measures.

Missing information 2: Lactation (IV zanamivir)

Non-clinical

In rats, zanamivir has been shown to be excreted into milk. However, there is no information on secretion into breast milk in humans.

Post-authorisation spontaneous reports

The available data from spontaneous reports on exposure for inhaled and IV zanamivir during breast- feeding do not suggest a safety risk to the infant from a nursing mother with this formulation. However, the inhalation dose is small (10mg, twice daily) and systemic exposure is minimal (4– 17%) compared with IV zanamivir.

Inhaled zanamivir

Population in need of further characterisation 1: Paediatric and Asian patients

In the Final Assessment Report of zanamivir EU-RMP version 03 (Procedure SE/H/PSUR/0017/004; December 2012), removal of these two categories of missing information was agreed with the Swedish MPA. GSK will remove Asians and paediatric populations from the inhaled zanamivir 'missing information' section of the next version of the EU-RMP, following completion of the Dectova procedure.

Population in need of further characterisation 2: Black and Hispanic populations (inhaled zanamivir)

Black and Hispanic populations were not specifically studied in the clinical development of zanamivir. Given the mechanism of action and pharmacokinetic characteristics of zanamivir, differences in efficacy in these populations in comparison to the subjects studied in the clinical development programme are unlikely.
A proposal for removal of Black and Hispanic populations as Missing Information will be provided in an updated EU-RMP after completion of the Dectova procedure.

Population in need of further characterisation 3: Pregnancy and Lactation (inhaled zanamivir)

Non-clinical reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs. There is no information on placental transfer in humans.

In rats, zanamivir has been shown to be excreted into milk. However, there is no information on secretion into breast milk in humans.

Reports of pregnancy and lactation from clinical trial or spontaneous sources regarding either the inhaled powder or IV formulations have not generated any safety signals to date. The systemic absorption of zanamivir administered as a powder inhalation (Diskhaler) is minimal (4 - 17% of an inhaled dose is absorbed systemically). It would therefore not be expected that an infant would be exposed to significant doses of zanamivir from a nursing mother receiving one of the inhaled powder formulations.

Population in need of further characterisation 4: Immunocompromised (inhaled zanamivir)

Immunocompromised subjects were not studied as part of the inhaled zanamivir clinical development program. Such patients are at higher risk from morbidity and mortality from any infectious disease, including influenza. Tolerability and surveillance of the safety of use of zanamivir in this population is followed by the routine PV.

As instructed by the MPA in the Final Assessment Report SE/H/180/RMP version 3.0, GSK will make available a review already conducted from spontaneous reports in immunocompromised patients in an updated EU-RMP after completion of the Dectova procedure.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14 Summary of safety concerns

Risk Category	Inhaled zanamivir	IV zanamivir
Important Identified Risks	None	None
Important Potential Risks	Neuropsychiatric events Antiviral resistance/lack of efficacy	Cardiac reactions (cardiac arrhythmias) Severe cutaneous reactions Hepatic failure Neuropsychiatric events Antiviral resistance/lack of efficacy
Missing Information	Paediatric and Asian Black and Hispanic patients Pregnancy and Lactation Immunocompromised patients	Use in Pregnancy Lactation

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine PV activities during a pandemic

In the event of an influenza pandemic, in addition to routine PV activities, GSK will undertake enhanced PV activities to address the anticipated volume of reports and the need to quickly identify and respond to any emerging safety signals.

When an influenza pandemic situation is declared, it is likely that there will be a large demand for inhaled and IV zanamivir. For IV zanamivir, this will lead to large exposure in subgroups of patients not studied during the clinical development programme, including pregnant and breast-feeding women. Therefore, it is of vital importance to collect and analyse the safety data in the zanamivir-treated population in near real time to rapidly detect any new safety signal that may arise.

It is also likely that, in the setting of increased use of zanamivir, there will be a high absolute number of adverse event reports, with many reports being submitted directly to regulatory authorities. In addition, it is anticipated that PV systems will be disrupted, with limited personnel available in both the industry and regulatory agencies. An accurate projection of the extent to which life and business activities will be disrupted during an influenza pandemic is not available. However, GSK has developed business continuity plans, which are regularly reviewed and updated, with the aim to provide continuity of operations for the various GSK departments in a crisis situation. These continuity plans encompass influenza pandemic diverse crisis scenarios and take into consideration European and WHO recommendations.

Enhanced pharmacovigilance activities during a pandemic

Previous pandemic PV activities have included:

- Increase in the intensity and frequency of safety signal detection and monitoring
- Aggregate data review e.g., monthly (or more frequently if indicated by the volume of incoming adverse event data)
- Optimal application of disproportionality analyses
- Close monitoring of important risks
- Frequent communication with regulatory agencies through simplified PSUR (S-PSUR) using, as a guide on content and frequency, ‘CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine.’; EMEA/359381/2009.
- Additional communication with the European Medicines Agency (IV zanamivir) and the Swedish Regulatory Agency (Reference Member State for inhaled zanamivir)
- For future pandemics, GSK will establish ways to capture adverse event information in addition to conventional spontaneous adverse reporting, using appropriate technologies e.g. via a company-sponsored web-site.

Important risks during a pandemic

In addition to the safety concerns identified in this EU-RMP, in a pandemic situation, when fewer direct contacts will be made between patients and health care providers, enhanced communication around the known risk of bronchospasm with inhaled zanamivir will also be required.

The risk of development of antiviral resistance/lack of efficacy will be particularly relevant in a pandemic situation where the number of patients receiving inhaled or IV zanamivir is likely to rapidly increase over a relatively short period of time. Neuraminidase susceptibility and development of drug resistance in influenza viruses continues to be monitored through a number of surveillance initiatives and ad hoc studies. The World Health Organisation (WHO) collates data from WHO National Influenza Centres and WHO Collaborating Centres, through the Global Influenza Surveillance and Response System. Data from Europe (EU/EEA) is collated by the coordinators of Community Network of Reference Laboratories for Human Influenza in Europe under the aegis of the ECDC. The early notification of resistance is crucial so that recommendations for patient management can be changed if anti-viral resistance emerges.

Spontaneous reports of lack of efficacy would be monitored as part of enhanced PV activities during any future pandemic. Whilst this may yield useful information GSK considers that the ISIRV-Antiviral Group experts and those of the WHO would be best placed to advise on and monitor susceptibility during a pandemic.

Summary of Areas of special interest during a pandemic

Areas of Special Interest (ASI) for enhanced surveillance during pandemic situations include the important potential risks for IV and inhaled zanamivir presented as safety concerns in this EU-RMP. For each of these ASI, any reported Individual Case Safety Reports will be prioritised for follow-up and evaluation during an influenza pandemic. These ASI include:

- Cardiac reactions (cardiac arrhythmias) [IV zanamivir]
- Neuropsychiatric events (inhaled and IV zanamivir)
- Severe cutaneous reactions (IV zanamivir)
- Hepatic failure (IV zanamivir)
- Bronchospasm (inhaled zanamivir)
- Use in pregnant women (inhaled and IV zanamivir)
- Use in breastfeeding women (IV zanamivir)
- Use in children
- Inhaled zanamivir age categories: <5y, 5-12y, 13-17y
- IV zanamivir age categories: <6mth, 6mth-<1y, 1-<2y, 2-<6y, 6-<13y, 13-<18y)
- Use in at risk groups
- inhaled zanamivir: patients with underlying chronic respiratory disease; immunocompromised patients
- IV zanamivir: immunocompromised patients
- Development of resistance/lack of efficacy (inhaled and IV zanamivir)
- Medication errors (inhaled and IV zanamivir)
- Fatal events (inhaled and IV zanamivir)

Specific adverse reaction follow-up questionnaires for severe cutaneous adverse reactions and hepatic failure

When reports are received from spontaneous sources, a Targeted Follow-up Questionnaire will be used for severe cutaneous reactions and hepatic failure (see Annex 4).

III.2 Additional pharmacovigilance activities

Inhaled zanamivir

No additional PV activities are considered to be required for inhaled zanamivir.

IV zanamivir

No additional PV activities are considered to be required for intravenous zanamivir.

III.3 Summary Table of additional Pharmacovigilance activities

There are no on-going or planned additional pharmacovigilance activities for Zanamivir 10mg/ml solution for infusion (IV zanamivir) and Zanamivir powder for inhalation (5mg).

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 15 Planned and on-going post-authorization efficacy studies that are conditions of the marketing authorization 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				
Retrospective observational chart review effectiveness study of IV zanamivir in ICU-treated influenza patients (Protocol ID: 208165)Ongoing	To compare using propensity score methods, all-cause in-hospital mortality in a group of ICU-admitted patients with influenza, who receive treatment with IV zanamivir as part of their clinical care with all-cause in-hospital mortality in a group of ICU patients who did not receive this therapy during the same influenza seasons and/or pandemic(s). To compare all-cause in-hospital mortality at 7, 10 and 14 days after IV zanamivir treatment initiation in the two groups.	To assess IV zanamivir when there is widespread use and no or limited other anti-influenza treatment options available. The ongoing real-world study will seek to assess the effectiveness of IV zanamivir in a patient population receiving routine clinical care, whilst seeking to minimise confounding by indication through propensity score methods.	Study start	The study was initiated on 03 Nov 2020. It is expected that enrolment will require multiple influenza seasons, depending circulating strains, vaccine coverage/effectiveness. Enrolment will complete after the intended study size is reached.
			Interim Report	Status to be reported to EMA annually within each annual re-assessment application.
			Final Report	The final study report will be available within 6 months after eCRF completion for the last subject.

Study status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are **Specific Obligations** in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Prospective, observational effectiveness study of IV zanamivir in patients with complicated influenza (Protocol ID: 212622) Ongoing	To compare using propensity score methods, all-cause in-hospital mortality in a group of hospitalised patients with influenza, who receive treatment with IV zanamivir as part of their clinical care with all-cause in-hospital mortality in a group of hospitalised patients who did not receive this therapy during the same influenza seasons and/or pandemic(s). To compare all-cause in- hospital mortality at 7, 10 and 14 days after IV zanamivir treatment initiation in the two groups.	To assess IV zanamivir when there is widespread use and no or limited other anti-influenza treatment options available.	Study start	Enrolment into the study will begin when specific conditions are met which may lead to a broader patient population receiving IV zanamivir. GSK envisages that such conditions would arise when European Public Health Clinical Practice Guidelines for the treatment of influenza recommend the early or first line use of IV zanamivir, such as during an influenza pandemic or when there is drug- resistant influenza (which remains susceptible to zanamivir) widely circulating in the European Union as reported by the European Reference Laboratory Network for Human Influenza (ERLI-Net).
			Interim reports	Status to be reported annually within each annual re-assessment application.
			Final Report	The final study report will be available within 6 months after eCRF completion for the last

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 16 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Cardiac reactions (cardiac arrhythmias) IV zanamivir	None
Severe cutaneous reactions IV zanamivir	SmPC section 4.4 and 4.8; PIL section 2 and 4
Hepatic failure IV zanamivir	Routine risk communication: SmPC section 4.8, PIL section 4
Neuropsychiatric Events Inhaled and IV zanamivir	Routine risk communication: Inhaled zanamivir SmPC section 4.4 PIL section 4, which contains a recommendation that parents should be especially careful to watch out for neuropsychiatric symptoms if their child or teenager has influenza. IV zanamivir SmPC section 4.4 and 4.8; PIL section 2 and 4
Antiviral resistance/lack of efficacy Inhaled and IV zanamivir	Routine risk communication SmPC section 4.4 and 5.1
Use in Pregnancy Inhaled and IV zanamivir	Routine risk communication: SmPC section 4.6 PIL section 2
Lactation Inhaled and IV zanamivir	Routine risk communication: SmPC section 4.6 PIL section 2

V.2 Additional Risk Minimization 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 minimization measures

Table 17 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac reactions (cardiac arrhythmias) IV zanamivir	None	Routine PV activities
Severe cutaneous reactions For IV zanamivir	Routine risk communication: SmPC 4.4 and 4.8; PIL section 2 and 4	Routine PV activities, including targeted follow-up of cases of SJS/TEN
Hepatic failure For IV zanamivir	Routine risk communication: SmPC section 4.8, PIL section 4	Routine PV activities, including targeted follow-up of Liver and Hepatobiliary adverse event reports
Neuropsychiatric events For Inhaled and IV zanamivir	Inhaled zanamivir Routine risk communication: SmPC section 4.4 and 4.8 PIL section 4 IV zanamivir Routine risk communication: SmPC section 4.4 and 4.8, PIL section 2 and 4	Routine PV activities
Antiviral resistance/lack of efficacy For Inhaled and IV zanamivir	Routine risk communication: SmPC section 4.4 and 5.1.	Routine PV activities
Use in Pregnancy For Inhaled and IV zanamivir	Routine risk communication: SmPC section 4.6 PIL section 2	Routine PV activities
Lactation For Inhaled and IV zanamivir	Routine risk communication: SmPC section 4.6 PIL section 2	Routine PV activities

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for DECTOVA (intravenous zanamivir)

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

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

This summary of the RMP for DECTOVA 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 DECTOVA's RMP.

I. The medicine and what it is used for

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.

Further information about the evaluation of DECTOVA's benefits can be found in DECTOVA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/dectova

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of DECTOVA, together with measures to minimise such risks and the proposed studies for learning more about DECTOVA'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 PIL 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 periodic safety update report (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 DECTOVA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of DECTOVA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.
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 DECTOVA. 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.

List of important risks and missing information	
Important identified risks	None
Important potential risks	Cardiac reactions (cardiacarrhythmias) Severe cutaneous reactions Hepatic failure Neuropsychiatric events Antiviral resistance/lack of efficacy
Missing information	Use in Pregnancy Lactation (drug exposure to the infant during breast-feeding)

II.B Summary of important risks

Important potential risk – Cardiac reactions (cardiac arrhythmias)	
Evidence for linking the risk to the medicine	The evidence for a causal association between IV zanamivir and cardiac arrhythmias is limited. There are in total 58 cases of arrhythmias reported, most reported in the CUP, but also three serious treatment-related cases in Phase II and Phase III trials. "Cardiac arrhythmias" is an adverse drug reaction stated in the SmPC for oseltamivir (Tamiflu SmPC). However, the scientific evidence for this is not apparent in the published literature, and there is insufficient evidence to suggest a class effect.
Risk factors and risk groups	Persons of any age with chronic cardiac disease (e.g. congestive cardiac failure) are at risk of complicated influenza which can result in exacerbation of their underlying illness.
Risk factors and risk groups	Cardiovascular involvement in influenza can occur through direct effects of the virus on the myocardium presenting as myocarditis, with associated electrocardiogram (ECG) changes, or through exacerbation of existing cardiovascular disease. Cardiovascular mortality is increased during influenza seasons in those patients with pre-existing coronary artery disease, and myocardial infarction rates have also been shown to increase during epidemics.
Risk minimisation measures	None

Important potential risk - Severe cutaneous reactions	
Evidence for linking the risk to the medicine	Post-marketing experience with the inhaled powder formulation of zanamivir (RELENZA); DECTOVA clinical trials; zanamivir aqueous solution Compassionate Use Programme (CUP). Severe skin reactions associated with RELENZA have been reported in the post-marketing period. These included Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme, bullous dermatitis and toxic skin eruption.
Risk factors and risk groups	Severe cutaneous reactions are known to be triggered by infectious agents. Therefore, patients with influenza and patients with concomitant infections may be at greater risk.
Risk minimisation measures	Routine risk communication: SmPC 4.4 and 4.8; PIL section 2 and 4

Important potential risk - Hepatic failure	
Evidence for linking the risk to the medicine	Hepatic failure cases (N= 8) have been reported in the CUP and assessed by the investigator as related to zanamivir. All cases were confounded by concomitant severe illness and concurrent medications. Increased liver function tests were reported in subjects receiving DECTOVA zanamivir across Phase I, II and III studies.
Risk factors and risk groups	Hepatic events have been primarily associated with DECTOVA (intravenous zanamivir), which has high systemic availability relative to RELENZA (zanamivir inhalation powder). DECTOVA is indicated for critically-ill hospitalised patients with complicated influenza, who may be at greater risk of hepatic events due to serious co-morbidities.
Risk minimisation measures	Routine risk communication: SmPC section 4.8 and PIL section 4.

Important potential risk - Neuropsychiatric events	
Evidence for linking the risk to the medicine	Spontaneous reports with RELENZA; Literature articles.
Risk factors and risk groups	Based on spontaneous reports with RELENZA, children and adolescents were identified as being at particular risk of neuropsychiatric events, particularly early in the influenza illness, and especially with concurrent pyrexia and/or influenza encephalopathy/encephalitis or underlying psychiatric disorder.
Risk minimisation measures	Routine risk communication: SmPC section 4.4 and 4.8; PIL section 2 and 4

Important potential risk - Antiviral resistance	
Evidence for linking the risk to the medicine	Post-authorisation RELENZA epidemiology study (OTH112321); clinical trials with DECTOVA; case studies in the medical literature for RELENZA and zanamivir aqueous solution from the Compassionate Use programme. To date, selection of resistance substitutions is rare and there is no evidence of emergence of clinically relevant resistance.
Risk factors and risk groups	Immunocompromised patients, off-label use.

Risk minimisation measures	Routine risk communication: SmPC section 4.4 and 5.1.

Missing information - Use in Pregnancy	
Risk minimisation measures	SmPC section 4.6; PIL section 2

Missing information - Lactation (drug exposure to the infant during breastfeeding)	
Risk minimisation measures	SmPC section 4.6; PIL section 2

II.C Post-authorization development plan

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

The following studies are conditions of the marketing authorisation:

Study/Activity (including study number)	**Objectives**	**Safety concerns/efficacy issue addressed**
Retrospective, observational chart review study on the effectiveness of IV zanamivir in intensive care unit (ICU)-treated influenza patients Study No. 208165	To compare using propensity score methods, all-cause in-hospital mortality in a group of ICU-admitted patients with influenza, who receive treatment with IV zanamivir as part of their clinical care with all-cause in-hospital mortality in a group of ICU patients who did not receive this therapy during the same influenza seasons and/or pandemic(s). To compare, using propensity score methods, all-cause in-hospital mortality at 7, 10 and 14 days after IV zanamivir treatment initiation in the two groups.	<u>Safety</u> Data on safety concerns of severe cutaneous reactions, hepatic failure, neuropsychiatric events, antiviral resistance/lack of efficacy, pregnancies via serious adverse event and adverse event reporting. <u>Efficacy</u> The generalizability of randomised controlled trial - based assessments of medical interventions may be limited by the restrictive entry criteria employed in such studies or their experimental nature. This real-world study will seek to assess the effectiveness of IV zanamivir in a patient population receiving routine clinical care, whilst seeking to minimise confounding by indication through propensity score methods.

Prospective, observational effectiveness study of IV zanamivir in patients with complicated influenza Study No. 212622	To compare using propensity score methods, all-cause in- hospital mortality in a group of hospitalised patients with complicated influenza, who receive treatment with IV zanamivir as part of their clinical care with all-cause in-hospital mortality in a group of hospitalised patients with complicated influenza who did not receive this therapy during the same influenza seasons and/or pandemic(s). To compare, using propensity score methods all-cause in-hospital mortality at 7, 10 and 14 days after IV zanamivir treatment initiation in the two groups.	Safety Data on safety concerns of severe cutaneous reactions, hepatic failure, neuropsychiatric events, antiviral resistance/lack of efficacy, pregnancies via serious adverse event and adverse event reporting. Efficacy The generalizability of randomised controlled trial - based assessments of medical interventions may be limited by the restrictive entry criteria employed in such studies or their experimental nature. This real-world study will seek to assess the effectiveness of IV zanamivir in a patient population receiving routine clinical care, whilst seeking to minimise confounding by indication through propensity score methods.

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

None

Summary of risk management plan for RELENZA (inhaled zanamivir)

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

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

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

I. The medicine and what it is used for

RELENZA is authorised for treatment of both influenza A and B in adults and children (≥ 5 years) who present with symptoms typical of influenza when influenza is circulating in the community.

RELENZA is also authorised for post-exposure prophylaxis of influenza A and B in adults and children (≥ 5 years) following contact with a clinically diagnosed case in a household. In exceptional circumstances, RELENZA may be considered for seasonal prophylaxis of influenza A and B during a community outbreak (e.g. in case of a mismatch between circulating and vaccine strains and a pandemic situation).

II. Risks associated with the medicine and activitiesto minimise of further characterise the risks

Important risks of RELENZA, together with measures to minimise such risks and the proposed studies for learning more about RELENZA'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 PIL 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 periodic safety update report (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 RELENZA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of RELENZA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.
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 RELENZA. 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.

List of important risks and missing information	
Important identified risks	None
Important potential risks	Neuropsychiatric events Antiviral resistance/lack of efficacy
Missing Information	Paediatric and Asian patients Use in Black and Hispanic patients Use in Pregnancy and Lactation Use in Immunocompromised patients

II.B Summary of important risks

Important potential risk - Neuropsychiatric events	
Evidence for linking the risk to the medicine	Spontaneous reports with RELENZA; Literature articles.
Risk factors and risk groups	Based on spontaneous reports with RELENZA, children and adolescents were identified as being at particular risk of neuropsychiatric events, particularly early in the influenza illness, and especially with concurrent pyrexia and/or influenza encephalopathy/encephalitis, or an underlying psychiatric disorder.
Risk minimisation measures	Routine risk communication: SmPC section 4.4 and 4.8; PIL section 4

Important potential risk - Antiviral resistance	
Evidence for linking the risk to the medicine	Post-authorisation RELENZA epidemiology study (OTH112321); case studies from the medical literature. To date, selection of resistance substitutions is rare and there is no evidence of emergence of clinically relevant resistance.
Risk factors and risk groups	Immunocompromised patients, Prophylactic use, off-label use.
Risk minimisation measures	Routine risk communication: SmPC section 5.1.

Missing information - Use in Pregnancy and Lactation (drug exposure to the infant during breast-feeding)	
Risk minimisation measures	SmPC section 4.6; PIL section 2

II.C Post-authorisation development plan

No further studies are planned for RELENZA.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following Targeted Follow-up Questionnaires are provided:

- Liver or Hepatobiliary events
- Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

GSK

Targeted Follow Up Questionnaire
Zanamivir & LIVER OR HEPATOBILIARY ADVERSE EVENTS

Patient, age, gender, initials:	**Sex/weight (is patient obese if weight unknown):**	**GSK CASE No:**

Lot Number & Expiration date (*for post-marketing reports only*):

Description of the Event:

	Yes	**No**
Are liver enzymes (ALT/SGPT, AST/SGOT, Alkaline Phosphatase, LDH, GGT or bilirubin (total, direct, or indirect bilirubin) or CPK elevated? If *yes,* please provide copies of results, including baseline and normal ranges:	☐	☐
Is patient symptomatic? *Please indicate all that apply.*		

☐ RUQ pain	☐ abdominal pain	☐ fever	☐ confusion
☐ nausea	☐ jaundice	☐ anorexia	☐ other:

Were any diagnostic imaging tests performed e.g., CT scan abdomen/ liver, abdominal ultrasound of liver/ hepatobiliary tree? If *yes*, please describe results or provide hard copy of results:	☐	☐
Was a liver biopsy performed? If *yes*, please describe results or provide copy of results:	☐	☐
Were any of the following laboratory tests performed? Prothrombin time, INR, Thrombin time, Partial thromboplastin time, Albumin, Total protein? If so, please provide a copy of the results.	☐	☐
If liver enzymes were abnormal, was serology for Hepatitis A, B, and C, obtained? If *yes*, please describe or provide copy of results:	☐	☐
Has the patient had close contact with a person with active hepatitis?	☐	☐

History:		
	Yes	**No**
Does the patient have right side heart failure?	☐	☐
Is there a history of prior liver disease (hepatitis A, B, C, hepatic failure or cirrhosis)?	☐	☐
Is there a history of Gilbert's Disease?	☐	☐
Is there a history of *recent* travel to a developing country?	☐	☐
Does the patient have history of autoimmune disease? If *yes*, please specify:	☐	☐
Does the patient have a history of any of the following? ☐ Active gall bladder disease ☐ Acute pancreatitis ☐ Alcohol use ☐ NSAID use ☐ IV drug use ☐ acetaminophen/paracetamol consumption in patients with chronic alcohol exposure -please state number of g/day taken:		
If diabetic, has the patient taken any of the following:. ☐ Avandia/ Avandamet ☐ Sulfonylureas ☐ Metformin ☐ Insulin ☐ Alpha-glucosidase inhibitors ☐ Repaglinide ☐ Troglitazone If *yes*, please give start and stop dates and dose:		

GSK

Targeted Follow Up Questionnaire

Zanamivir & STEVENS JOHNSON SYNDROME/ TOXIC EPIDERMAL NECROLYSIS

Patient, age, gender, initials:	**Sex/weight (is patient obese if weight unknown):**	**GSK CASE No:**

Lot Number & Expiration date (*for post-marketing reports only*):

Description of the Event:

Please provide a full description of the lesion (i.e. erythematous, vesicular, pustular, target lesions).

Which parts of the body were affected?

	Yes	No
Was there desquamation (skin loss)? Estimate the percentage of the body surface area involved:	☐	☐
Was there any involvement of the mucus membranes? If *yes*, please describe:	☐	☐
Was the rash associated with other systemic symptoms or abnormalities? If *yes*, please describe:	☐	☐

Who made the diagnosis? ☐ General Practitioner ☐ Dermatologist ☐ Other

Diagnostic Tests: *Please attach all applicable.*

	Attached	
▪ Please provide significant laboratory results	☐	
	Yes	**No**
▪ Was a skin biopsy done? If *yes*, please attach results:	☐	☐

History:

	Yes	No
Does the patient have a history of previous allergies to drugs? If *yes,* please list:	☐	☐
Has the patient had a recent infection (e.g., herpes simplex, streptococcal or staphylococcal infection, mycoplasma pneumonia)? If *yes*, please specify:	☐	☐

Does the patient take any of the following medications?

	Yes	No		Yes	No
Anticonvulsants	☐	☐	Barbiturates	☐	☐

Sulfonamides	☐	☐	NSAIDs (e.g., Naproxen)	☐	☐
Penicillins	☐	☐	Allopurinol	☐	☐

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.