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 agents other than zanamivir, and/or
- Other anti-viral agents 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/summaries-opinion/dectova

II. Risks associated with the medicine and activities to minimise or further characterise 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 (cardiac arrhythmias) 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 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.
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. 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=5) 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
Additional pharmacovigilance activities	Post-authorisation Pregnancy Registry study See section VI.3.3 of this summary for an overview of the post-authorisation development plan.

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

II.C Post-authorisation development plan

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

The following studies are conditions of the marketing authorisation:

Study/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.

Study/Activity (including study number)	Objectives	Safety concerns/efficacy issue addressed
Prospective, observational effectiveness study of IV zanamivir in patients with complicated influenza Study No. TBD	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.	<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.

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

Study/Activity (including study number)	Objectives	Safety concerns/efficacy issue addressed
Zanamivir 10mg/ml solution for infusion pregnancy registry: an observational study of the safety of zanamivir 10mg/ml solution for infusion exposure in pregnant women with complicated influenza and their offspring. Protocol ID: 208140 PASS Category 3	To evaluate pregnancy outcomes among women with complicated influenza exposed to IV zanamivir at any time during pregnancy.	Use in pregnancy and effects on the foetus.