ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Alpivab 200 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial of concentrate contains 200 mg peramivir.
1 mL concentrate for solution for infusion contains 10 mg peramivir (anhydrous base).

Excipients with known effect

Each mL of concentrate contains 0.154 millimole (mmol) sodium, which is 3.54 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alpivab is indicated for the treatment of uncomplicated influenza in adults and children from the age of 2 years (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Posology

Alpivab should be administered as a single intravenous dose within 48 hours of the onset of symptoms of influenza.

The recommended single intravenous dose of peramivir depends on age and body weight as shown in Table 1.

Table 1: Peramivir dose based on age and body weight

Age and body weight	**Recommended single dose**
Children aged from 2 years and <50 kg	12 mg/kg
Children aged from 2 years and ≥50 kg body weight	600 mg
Adults and adolescents (13 years and older)	600 mg

Elderly
No dose adjustment is required based on age (see sections 4.4 and 5.2).

Renal impairment
The dose should be reduced for adults and adolescents (13 years and older) with absolute glomerular filtration rate (GFR) below 50 mL/min as shown in Table 2 (see sections 4.4 and 5.2).

Table 2: Peramivir dose for adults and adolescents (from 13 years and 50 kg) based on absolute GFR

Absolute Glomerular Filtration Rate (GFR)*	Recommended single dose
≥50	600 mg
30 to 49	300 mg
10 to 29	200 mg

*Absolute GFR not adjusted for body surface area

In adults and adolescents (from 13 years and 50 kg) with chronic renal impairment maintained on haemodialysis, peramivir should be administered after dialysis at a dose adjusted for renal function (Table 2).

There are insufficient clinical data available in children and adolescents aged less than 13 years or with body weight less than 50 kg with renal impairment to be able to make any dosing recommendation.

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of peramivir in children aged under 2 years has not yet been established. No data are available.

Method of administration

Alpivab is administered via intravenous infusion for 15 to 30 minutes.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Serious hypersensitivity reactions

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

Neuropsychiatric events

Delirium, hallucinations and abnormal behaviour have been reported in patients with influenza who were receiving peramivir. These events were reported primarily among paediatric patients and often had an abrupt onset and rapid resolution. The contribution of peramivir to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behaviour.

Reduced renal function

Acute renal failure, renal failure, pre-renal failure, renal disorder, anuria, nephritis, and increased blood creatinine have been reported in patients with influenza who were receiving peramivir. Most of the cases occurred in elderly patients with comorbidities and multiple concomitant medicinal products. The contribution of peramivir to these events has not been established. Patients with influenza and already existing diseases should be closely monitored for renal function.

Limitations of the clinical data

The efficacy of peramivir as a single dose treatment for uncomplicated influenza was demonstrated in a single placebo-controlled study conducted in 300 adult patients in Japan during the 2007/2008 influenza season. The recommended 600 mg single intravenous dose resulted in shortening of the median time to alleviation of symptoms by 21 hours (see section 5.1).

Available data do not support a conclusion that peramivir is effective in patients with influenza B or in patients with complicated influenza.

Resistance to peramivir

Influenza A/H1N1 viruses that contain the H275Y mutation have reduced susceptibility to peramivir and oseltamivir. In a clinical trial, no statistically significant clinical benefit could be demonstrated for peramivir over placebo in patients infected with the A/H1N1 virus containing the H275Y mutation. Available information on influenza drug susceptibility should be taken into account when deciding whether to use peramivir (see section 5.1).

Risk of bacterial infections

There is no evidence for efficacy of peramivir in any illness caused by agents other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Peramivir has not been shown to prevent such complications.

Excipients

This medicinal product contains 212.4 mg sodium per 3 vials, equivalent to 10.6% of the World Health Organization (WHO) recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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

Live attenuated influenza vaccines are not recommended to be used until 48 hours following Alpivab administration due to a theoretical risk that peramivir could reduce the immunogenicity of the vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancies outcomes) from the use of peramivir in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of peramivir during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of peramivir in milk (see section 5.3).

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from peramivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of peramivir on fertility are available. Peramivir had no effects on mating or fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most important serious adverse reactions associated with peramivir in patients are anaphylaxis and skin reactions, including erythema multiforme and Stevens-Johnson Syndrome.
Among 467 adult subjects with uncomplicated influenza who received a single intravenous dose of peramivir 600 mg in clinical trials, the most commonly observed adverse reactions were neutrophil count decreased (3.2 %) and nausea (2.4 %).

Tabulated list of adverse reactions

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 3: Adverse reactions in studies investigating peramivir for treatment of uncomplicated influenza in adults

System Organ Class (SOC)	Adverse Reaction According to Frequency*			
	Common	**Uncommon**	**Rare**	**Unknown**
Blood and lymphatic system disorders	neutrophil count decreased			
Immune system disorders				anaphylactic reaction*, anaphylactic shock*

System Organ Class (SOC)	Adverse Reaction According to Frequency*			
	Common	**Uncommon**	**Rare**	**Unknown**
Metabolism and nutrition disorders	blood lactate dehydrogenase increased	decreased appetite, blood albumin decreased, blood chloride increased, blood glucose decreased, blood lactate dehydrogenase decreased, blood potassium increased, blood sodium increased, blood uric acid increased, protein total increased		
Psychiatric disorders		insomnia		abnormal behaviour*, delirium*
Nervous system disorders		hypoaesthesia, paraesthesia		
Eye disorders		vision blurred		
Cardiac disorders		electrocardiogram QT prolonged		
Gastrointestinal disorders	nausea, vomiting	abdominal pain upper, abdominal discomfort, gastritis		
Hepatobiliary disorders		increased gamma-glutamyltransferase		liver disorder*, alanine aminotransferase increased*, aspartate aminotransferase increased*
Skin and subcutaneous tissue disorders		dermatitis, drug eruption, eczema, urticaria	erythema multiforme	dermatitis exfoliative*, Stevens-Johnson syndrome*
Musculoskeletal and connective tissue disorders		arthralgia, blood creatine phosphokinase increased		
Renal and urinary disorders		blood urea increased, blood present in urine, urobilin present in urine, blood creatinine increased, urine ketone body increased		acute kidney injury*, renal impairment*
General disorders and administration site conditions		chest discomfort, fatigue		

*These events reported from post-authorization use occurred with different dosage and dosing schedule to that described in the SmPC.

Paediatrics

In paediatric subjects (age 2 to 17 years) with uncomplicated influenza enrolled in a clinical trial, the safety profile of peramivir was similar to that reported in adults. Common adverse reactions not reported in adults were injection site rash, pyrexia, tympanic membrane hyperaemia, psychomotor hyperactivity, and pruritus.

Reporting of suspected adverse reactions

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

4.9 Overdose

There is no experience of acute overdose with peramivir in humans. Treatment of an overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

Peramivir is cleared by renal excretion and can be cleared by haemodialysis. There is no specific antidote to treat an overdose of this medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code**:** J05AH03

Mechanism of action

Peramivir is an inhibitor of influenza virus neuraminidase, an enzyme that releases viral particles from the plasma membrane of infected cells and is also important for viral entry into uninfected cells, which causes further spread of infectious virus in the body.

In-vitro activity

Neuraminidase inhibition occurred at very low peramivir concentrations *in-vitro*, with median inhibitory concentration 50% (IC_{50}) values of 0.13 nanomolar (nM) to 0.99 nM against influenza A and B strains.

Resistance
In a clinical trial in which 245 subjects were infected at baseline with influenza A/H1N1 containing the H275Y mutation, the median baseline IC_{50} values for peramivir, oseltamivir and zanamivir were 51.0 nM, 487.6 nM and 0.95 nM, respectively.

In clinical trials, H275Y was the only resistance-associated treatment-emergent mutation in the neuraminidase gene that occurred in virus obtained from more than one peramivir-treated subject (in 9 of 481[1.9 %] infected with the A/H1N1 influenza virus).

Cross resistance
The H275Y substitution is associated with reduced susceptibility to peramivir and oseltamivir. Cross-resistance between peramivir and each of oseltamivir and zanamivir may also occur.

Clinical studies

Uncomplicated influenza in adults

A randomised, multicentre, double-blind trial conducted in Japan evaluated a single intravenous administration of peramivir 300 mg or 600 mg, or placebo administered over 30 minutes in subjects 20 to 64 years of age with uncomplicated influenza. Subjects were eligible if they had fever greater than 38 °C and a positive rapid antigen test for influenza virus, accompanied by at least two of the following symptoms: cough, nasal symptoms, sore throat, myalgia, chills/sweats, malaise, fatigue or headache.

Study treatment was started within 48 hours of onset of symptoms. Subjects participating in the trial were required to self-assess their influenza symptoms as "none', 'mild', 'moderate' or 'severe' twice daily. The primary endpoint, time to alleviation of symptoms, was defined as the number of hours from initiation of study drug until the start of the 24 hour period in which all seven symptoms of influenza (cough, sore throat, nasal congestion, headache, feverishness, myalgia and fatigue) were either absent or present at a level no greater than mild for at least 21.5 hours.

The intent to treat influenza population (ITTI) included 296 subjects with influenza confirmed by polymerase chain reaction (PCR). Among the 97 subjects enrolled in the peramivir 600 mg dose group, 99 % were infected with influenza A virus (subtypes H1 and H3; 71 % and 26 %, respectively) and 1 % with influenza B virus. At enrollment 85 % of the 296 subjects had a composite influenza symptom score <15. The mean temperature at enrolment was 38.6 °C (axillary). Key efficacy results are presented in Table 4.

Table 4: Key efficacy results from study 0722T0621 (ITTI Population)

	Peramivir 600 mg n=97	**Placebo** n=100
Time to alleviation of symptoms median (hours) (95 % CI)	59.0 (54.4, 68.1)	81.8 (68.0, 101.5)
Time to recovery of normal temperature median (hours) (95 % CI)	30.2 (25.9, 31.9)	42.4 (32.9, 46.5)

CI = Confidence Interval

Uncomplicated influenza in paediatric subjects aged 2-17 years
The safety of peramivir was evaluated in a randomised, active-controlled study of 110 subjects with uncomplicated influenza who received open label treatment with a single dose of peramivir (600 mg for subjects 13 to 17 years of age and 12 mg/kg up to a maximum dose of 600 mg in subjects 2 to 12 years of age) or oral oseltamivir administered twice daily for 5 days. The ITTI population included 84 subjects with influenza confirmed by PCR. Among the 93 subjects enrolled in the peramivir dose group, 43% were infected with influenza A virus (subtypes H1 and H3; 54 % and 46 %, respectively) and 27% with influenza B virus. Randomisation was 4:1 for peramivir and oseltamivir. Treatment was given or commenced within 48 hours of onset of symptoms of influenza. Efficacy (time to resolution of fever; time to resolution of influenza symptoms, viral shedding, virus susceptibility) was a secondary endpoint.

Subjects receiving peramivir experienced a median time to alleviation of their combined influenza symptoms of 79.0 hours and the median time to recovery to normal temperature (less than 37 °C) was approximately 40.0 hours.

Elderly patients
Clinical trials in which single intravenous doses of peramivir were administered to patients with uncomplicated influenza included few subjects aged 65 and over (n=10).

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

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetic parameters following intravenous (IV) administration of peramivir (0.17 to 2 times the recommended dose) showed a linear relationship between dose and exposure parameters (maximum serum concentration [C_{max}] and area under the curve [AUC]). Following intravenous administration of a single dose of peramivir 600 mg over 30 minutes, C_{max} was reached at the end of infusion.

Distribution

In-vitro binding of peramivir to human plasma proteins is less than 30 %.
Based on a population pharmacokinetic analysis, the central volume of distribution was 12.56 L.

Biotransformation

Peramivir is not significantly metabolised in humans.

Elimination

The elimination half-life of peramivir following IV administration to healthy subjects of 600 mg as a single dose is approximately 20 hours. The major route of elimination of peramivir is via the kidney. Renal clearance of unchanged peramivir accounts for approximately 90 % of total clearance.

Special populations

Race
In simulations of a single dose of 600 mg, the predicted AUC in Asians (AUC_{0-24} 88,800 ng•h/mL) was slightly higher as compared to Non-Asians (AUC_{0-24} 77,200 ng•h/mL).

Gender
The pharmacokinetics of peramivir following a 600 mg intramuscular (IM) injection was similar in males and females with $AUC_{0-\infty}$ of 76,600 ng•hr/mL and 101,000 ng•hr/mL, respectively, and C_{max} of 27,760 ng/mL and 34,710 ng/mL, respectively.

Paediatrics
The pharmacokinetics of peramivir has been evaluated in a study in paediatric subjects 2 to 17 years of age with uncomplicated influenza. Pharmacokinetic sampling in this study was limited to approximately 3 hours after administration of peramivir. Pharmacokinetics of peramivir in subjects 2 to 17 years of age (administered 12 mg/kg or 600 mg according to age and body weight) and in healthy adults (administered 600 mg) was similar (Table 5).

Table 5: Pharmacokinetic parameters in paediatric subjects

Age Group		N	C_{max} (ng/mL)	AUC_{last} (ng•h/mL)
2 years - <7 years	Mean (SD)	28	53,600 (26,200)	74,000 (30,000)
	Geometric Mean		47,400	68,100
	%CV		48.9	40.6
7 years - <13 years	Mean (SD)	39	66,800 (35,400)	87,000 (40,800)
	Geometric Mean		61200	81,000
	%CV		53.0	46.8
13 years - <18	Mean (SD)	20	54,300 (17,900)	72,400 (20,000)

	Geometric Mean		51,500	69,500
	%CV		33.0	27.6
2 years - <18 years	Mean (SD)	87	59,700 (29,700)	79,500 (34,000)
	Geometric Mean		54,200	74,000
	%CV		49.8	42.7

SD = Standard Deviation; CV = Coefficient of Variation

Elderly
The pharmacokinetics of peramivir was evaluated in 20 elderly subjects (>65 years of age) following a single 4 mg/kg IV dose of peramivir. The elderly subjects enrolled were aged 65 to 79 years, with a mean age of 70.1 years, with creatinine clearance (Cockcroft-Gault calculation) $CrCl_{cg}$ ranging from 82.8 mL/min to 197.9 mL/min. The pharmacokinetics in elderly subjects was similar to non-elderly subjects. Mean peak concentrations of peramivir were approximately 10 % higher in elderly subjects following administration of a single dose when compared to young adults (22,647 vs. 20,490 ng/mL, respectively). Exposure (AUC_{0-12}) to peramivir following a single dose was approximately 33 % higher in elderly subjects compared to young adults (61,334 vs. 46,200 ng•hr/mL, respectively).

Renal impairment
In a study in subjects with various degrees of renal impairment and subjects with normal renal function, a single 2 mg/kg IV dose of peramivir was administered. Serum creatinine measurements were used to calculate creatinine clearance (Cockcroft-Gault equation). The mean $AUC_{0-\infty}$ was increased by 28 %, 302 % and 412 % in subjects with creatinine clearance of 50-79, 30-49 and 10-29 mL/min, respectively. Haemodialysis initiated at 2 hours after dosing reduced systemic exposure of peramivir by 73 to 81 %.

Hepatic impairment
The pharmacokinetics of peramivir in subjects with hepatic impairment has not been studied. No clinically relevant alterations to peramivir pharmacokinetics are expected in patients with hepatic impairment based on the route of peramivir elimination.

5.3 Preclinical safety data

Peramivir was not teratogenic in embryo-fetal development studies in rats and rabbits and had no effects on mating or fertility in rats up to 600 mg/kg/day, at which exposures were approximately 8-fold of those in humans at the clinically recommended dose. However, in an embryo-foetal development study in rats in which dams received continuous infusions of peramivir from day 6-17 of gestation at doses of 50, 400 or 1000 mg/kg/day, dose related increases in the incidences of reduction of the renal papilla and dilatation of the ureters were observed. The teratological importance of these findings is unclear.

Carcinogenicity studies by intravenous injection of peramivir were not performed.

Peramivir was not mutagenic or clastogenic in a battery of *in-vitro* and *in-vivo* assays.

Acute renal necrosis was found in rabbits at doses ≥ 200 mg/kg with a clear no observed adverse effect level (NOAEL) established in multiple studies at 100 mg/kg/day.

Two-week oral toxicity studies were conducted in juvenile rats and rabbits, and a four-week IV toxicity study was conducted in juvenile rats. In general, nephrotoxicity was observed in rabbits, no unexpected toxicity was observed, and no other target organ toxicity was identified in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

5 years

After dilution

Chemical and physical in-use stability has been demonstrated for 72 hours at 5 ºC and 25 ºC.
From a microbiological point of view, the product, once diluted, should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ºC to 8 ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not refrigerate or freeze.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear glass vial (Type I) with a coated bromobutyl-rubber stopper, aluminium overseal and flip-off cap.

Pack size of 3 single-use vials.

6.6 Special precautions for disposal and other handling

Aseptic technique should be used during the preparation of Alpivab to prevent inadvertent microbial contamination.

The following steps should be followed to prepare a diluted solution of peramivir:

- Check the seal of each vial. Do not use if seal opening is broken or missing.
- Visually inspect the peramivir concentrate 10 mg/mL. It must be colourless and without particulate matter.
- If a patient receives 600 mg peramivir the required volume of peramivir concentrate is 60 mL (3 vials with 20 mL each). In the case of a 300 mg peramivir dose, 30 mL (1½ vials) of peramivir concentrate is needed and for a 200 mg dose, only 20 mL (1 vial). Fractions of a vial may be needed for appropriate dose adjustments in children with a bodyweight of less than 50 kg.
- Add the measured volume of peramivir concentrate into the infusion container.
- Dilute the required dose of peramivir concentrate in sodium chloride 9 mg/mL (0.9 %) or 4.5 mg/mL (0.45 %) solution for infusion, 5 % dextrose or Ringer lactate solution to a volume of 100 mL.
- Administer the diluted solution via intravenous infusion for 15 to 30 minutes.

- Once a diluted peramivir solution has been prepared, administer immediately or store in a refrigerator (2 °C to 8 °C) for up to 24 hours. If refrigerated, allow the diluted peramivir solution to reach room temperature, then administer immediately.
- Discard any unused diluted solution of peramivir after 24 hours.

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

7. MARKETING AUTHORISATION HOLDER

BioCryst Ireland Limited
Atlantic Avenue
Westpark Business Campus
Shannon
V14 YX01
Ireland
Tel: +353 1223 3541
E-mail: safety@biocryst.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1269/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/04/2018

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

Seqirus Vaccines Ltd
Gaskill Road
Speke
Liverpool
L24 9GR
UNITED KINGDOM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Alpivab 200 mg concentrate for solution for infusion
peramivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL concentrate contains 10 mg peramivir (anhydrous basis).
Each 20 mL vial contains 200 mg peramivir.

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
3 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

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

--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioCryst Ireland Limited
Atlantic Avenue
Westpark Business Campus
Shannon
V14 YX01
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1269/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Alpivab 200 mg concentrate for solution for infusion
peramivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL concentrate contains 10 mg peramivir (anhydrous base).
Each 20 mL vial contains 200 mg peramivir.

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

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

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BioCryst Ireland Limited
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V14 YX01
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1269/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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15. INSTRUCTIONS ON USE

--

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Alpivab 200 mg concentrate for solution for infusion
peramivir

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alpivab is and what it is used for

Alpivab contains the active substance peramivir which belongs to a group of medicines called neuraminidase inhibitors. These medicines prevent the influenza virus from spreading inside the body.

Alpivab is used to treat adults and children aged from 2 years with influenza that is not severe enough to require hospitalisation.

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

You must not receive Alpivab

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

Warnings and precautions

Talk to your doctor or pharmacist before you are given Alpivab if you have reduced kidney function. Your doctor may have to adjust your dose.

Tell your doctor immediately if you experience serious skin or allergic reactions after Alpivab is given. Symptoms may include skin or throat swelling, difficulty breathing, blistering rash or peeling skin. See section 4.

Tell your doctor immediately if you experience abnormal behaviour after Alpivab is given. Symptoms may include confusion, difficulty thinking or hallucinations. See section 4.

Children and adolescents

Alpivab is not recommended in children aged under 2 years.

Other medicines and Alpivab

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Live attenuated influenza vaccines should not be given until 48 hours after treatment with Alpivab. This is because Alpivab may prevent these vaccines from working well enough.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or breast-feeding. Your doctor will advise on whether you can be given Alpivab during pregnancy, or whether you are to stop breast-feeding for a short period after getting Alpivab.

Driving and using machines

Alpivab is not likely to change your ability to drive and use machines.

Alpivab contains sodium

This medicine contains 212.4 mg sodium (main component of cooking/table salt) in each dose consisting of 3 vials. This is equivalent to 10.6 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How Alpivab is given

Alpivab is given by a healthcare profesional as a single dose within 2 days of the start of influenza symptoms. It is first diluted and then given into a vein by infusion (drip), over 15 to 30 minutes.

- Adults and adolescents (13 years and older) receive 600 mg (3 Alpivab vials).
- Children aged from 2 years weighing 50 kg or more receive 600 mg (3 Alpivab vials).
- Children aged from 2 years weighing less than 50 kg receive 12 mg per kg body weight.
- Patients with reduced kidney function may require a reduced dose.

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

4. Possible side effects

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

Contact your doctor immediately if any of the following side effects occur:

Rare, may affect up to 1 in 1,000 people
- severe skin rash with or without blisters and fever

Not known, frequency cannot be estimated from the available data
- very severe skin reactions, including Steven-Johnson syndrome and dermatitis exfoliative These skin reactions are life-threatening rashes with fever and blisters and can effect the lining of the mouth and genitals.
- severe allergic reactions, including severe allergic shock reaction with features such as itchy rash, swelling of the throat and tongue, breathing difficulty, lightheadedness and vomiting

Other side effects occur with the following frequencies:

Common, may affect up to 1 in 10 people
- low levels of a white blood cell type called neutrophils
- blood tests showing increased levels of lactate dehydrogenase
- nausea (feeling sick), vomiting

Uncommon, may affect up to 1 in 100 people
- decreased appetite
- blood tests showing decreased levels of albumin, glucose, lactate dehydrogenase
- blood tests showing increased levels of chloride, potassium, sodium, uric acid, protein total, gamma-glutamyltransferase, creatine phosphokinase, urea, creatinine
- sleeplessness
- reduced sense of touch or sensation
- abnormal sensation such as prickling, tingling and itchiness
- blurred vision
- prolonged time of the heart ventricle activity, measured in the ECG
- upper abdominal pain, abdominal discomfort
- inflammation of stomach lining
- skin inflammation, eczema, rash, nettle-rash
- joint pain
- urobilin presented in the urine
- increased level of urine ketone body
- chest discomfort, fatigue

Not known, frequency cannot be estimated from the available data
- abnormal behaviour, delirium
- liver disorder
- blood test showing increased levels of alanine aminotransferase, aspartate aminotransferase
- acute kidney injury, reduced kidney function

Children and Adolescents from 2 years
Side effects were similar to adults but also included the following:
Common, may affect up to 1 in 10 people
- rash on the injection site
- fever
- red ear drum
- restlessness
- itching

Reporting of side effects

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

5. How to store Alpivab

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

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

Do not refrigerate or freeze.

Once diluted, administer the prepared Alpivab solution immediately; otherwise, store in a refrigerator (2 °C – 8 °C) for up to 24 hours.

6. Contents of the pack and other information

What Alpivab contains

- The active substance is peramivir.
  Each 20 mL vial contains 200 mg peramivir. 1 mL concentrate for solution for infusion contains 10 mg peramivir (anhydrous base).
- The other ingredients are sodium chloride, water for injections, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment).

What Alpivab looks like and contents of the pack

Alpivab is a clear, colourless, sterile concentrate for solution for infusion. It is provided in a clear glass vial with a coated rubber stopper, aluminium overseal and flip-off cap.

Each carton contains 3 vials.

Marketing Authorisation Holder
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Shannon
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Manufacturer
Seqirus Vaccines Limited
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UK

This leaflet was last revised in {**MM/YYYY**}.

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

The following information is intended for healthcare professionals only:

Use aseptic technique during the preparation of Alpivab to prevent microbial contamination. There is no preservative or antibacterial agent in the solution. Do not mix or co-infuse Alpivab with other medicines administered into a vein.

Follow the steps below in the provided order to prepare a diluted solution of Alpivab:
1. Check the seal of each vial. Do not use if the seal opening is broken or missing.
2. Inspect the Alpivab concentrate. It must be colourless and without particulate matter.
3. If a patient receives 600 mg peramivir the required volume of Alpivab concentrate is 60 mL (3 vials of 20 mL each). In the case of a 300 mg peramivir dose, 30 mL (1½ vials) of Alpivab concentrate

is needed and for a 200 mg dose, only 20 mL (1 vial). Fractions of a vial may be needed for appropriate dose adjustments in children with a bodyweight of less than 50 kg.
4. Add the measured volume of Alpivab concentrate into the infusion container.
5. Dilute the required dose of Alpivab concentrate in sodium chloride 9 mg/mL (0.9 %) or 4.5 mg/mL (0.45 %) solution for infusion, 5 % dextrose or Ringer lactate solution to a volume of 100 mL.
6. Administer the diluted solution via intravenous infusion over 15 to 30 minutes.
7. Once a diluted Alpivab solution has been prepared, administer immediately or store in a refrigerator (2 °C to 8 °C) for up to 24 hours. If refrigerated, allow the diluted Alpivab solution to reach room temperature, then administer immediately.
8. Discard any unused diluted solution of Alpivab after 24 hours.

No special requirements for disposal.

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