ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aqneursa 1 g granules for oral suspension in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 1 g levacetylleucine.

Excipients with known effect

Each sachet contains 642.2 mg isomalt and 0.153 mg propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension.

White to off-white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aqneursa is indicated for the treatment of neurological manifestations of Niemann-Pick type C (NPC) disease, in combination with miglustat, or as a monotherapy in patients where miglustat is not tolerated, in adults and children aged 6 years and older and weighing at least 20 kg.

4.2 Posology and method of administration

Posology

Adults and paediatric population aged 6 years and older and weighing at least 20 kg
The recommended dose is based on the patient's body weight in kg according to Table 1. Food and drink should be avoided 0.5 hours before and 2 hours after administration (see section 5.2).

Table 1: Recommended dose

Patient's body weight	Morning dose	Afternoon dose	Evening dose
20 to 24 kg	1 g (1 sachet)	No dose	1 g (1 sachet)
25 to 34 kg	1 g (1 sachet)	1 g (1 sachet)	1 g (1 sachet)
35 kg or more	2 g (2 sachets)	1 g (1 sachet)	1 g (1 sachet)

If a dose is missed, it should be skipped, and the next dose should be taken as scheduled.

Paediatric population aged less than 6 years or weighing under 20 kg
The safety and efficacy of Aqneursa in children aged less than 6 years or weighing under 20 kg have not yet been established. No data are available.

Method of administration

Oral use with liquid
The content of one sachet should be poured into 40 mL (3 tablespoons) of water and stirred until fully dispersed. Using hot liquid is not recommended. The entire suspension should be drunk immediately after preparation (within 30 minutes). If the suspension is not drunk immediately, it should be stirred again before intake. A visible amount of residual suspension may remain after the suspension has been consumed; no additional rinsing should be performed in this case.

All steps must be repeated if a second sachet is required.

Administration via gastrostomy tube
Aqneursa may be administered via gastrostomy tube (French size 18 or larger). The content of one sachet should be emptied into a container with 40 mL of water and mixed until all the granules are dispersed. Afterwards, the suspension should be drawn up into a catheter tip syringe. The content of the syringe is dispensed into the gastrostomy tube by applying steady pressure. Afterwards, the dosing syringe is refilled with water and the tube flushed with at least 20 mL of water. The suspension should be used immediately (within 30 minutes).

See section 6.6 “Further information on administration through gastrostomy tube”.

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

Anaphylaxis and hypersensitivity reactions

Although no patient experienced anaphylactic or hypersensitivity reaction during the clinical studies, anaphylactic and hypersensitivity reactions may occur after administration of levacetylleucine. Immediate discontinuation of Aqneursa and necessary emergency treatment is required if such reactions occur.

Excipients

Each sachet contains 642.2 mg isomalt. Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

This medicinal product contains 0.153 mg propylene glycol in each sachet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Interactions with levacetylleucine

An interaction of levacetylleucine (N-acetyl-L-leucine) with N-acetyl-DL-leucine and N-acetyl-D-leucine has been identified in pharmacology studies indicating that N-acetyl-D-leucine may compete with levacetylleucine for uptake by the monocarboxylate transporters. Concomitant use of levacetylleucine with N-acetyl-DL-leucine and N-acetyl-D-leucine should be avoided.

Interactions with substrates of transporters P-gp, BCRP or BSEP

Levacetylleucine may be an inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) or bile salt export pump (BSEP) (see section 5.2). The relevance to humans is uncertain. A potential interaction of levacetylleucine with other medicinal products that are substrates of P-gp (e.g. digoxin, dabigatran, loperamide, irinotecan, doxorubicin, vinblastine, paclitaxel, fexofenadine, seliciclib, quinidine, talinolol), BCRP (e.g. sulfasalazine, rosuvastatin) or BSEP cannot be excluded.

Caution should be exercised when levacetylleucine is co-administered with BSEP substrates.

The potential inhibitory effect of levacetylleucine on multidrug and toxin extrusion proteins (MATE) transporters is unknown; therefore, caution is advised when co-administering levacetylleucine with substrates of MATE transporters.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of levacetylleucine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Aqneursa is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether levacetylleucine or metabolites of levacetylleucine are excreted in human milk. A risk to the newborns and infants cannot be excluded.
A decision must be made as to whether to discontinue breast-feeding or to discontinue/abstain from Aqneursa 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 levacetylleucine on fertility is available. Animal studies indicate no effects of levacetylleucine on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The most common adverse reaction, with a frequency of 1.2%, is flatulence.

Tabulated list of adverse reactions

Adverse reactions observed during the placebo-controlled, randomised, crossover clinical study and the open-label, rater-blinded study, including extension phase, in patients with NPC are based on a total of 84 patients with a median treatment duration of 86 days.

Within the system organ classes, adverse reactions are listed according to the following frequency categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100),

rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 2: Adverse reactions in patients with Niemann-Pick Type C treated with levacetylleucine

System Organ Class	Frequency	Adverse reaction
Gastrointestinal disorder	Common	Flatulence

Reporting of suspected adverse reactions

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

4.9 Overdose

In case of overdose, symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX27.

Pharmacodynamic effects

Aqneursa contains levacetylleucine that targets underlying processes of neurological dysfunction. Nonclinical studies demonstrated that levacetylleucine corrects energy metabolism, including improving adenosine triphosphate production.

Clinical efficacy and safety

The efficacy and safety of levacetylleucine for treatment of NPC was studied in a randomised, double-blind, placebo-controlled, 2-period crossover study that evaluated the efficacy of levacetylleucine in NPC patients. To be eligible for the study, patients had to be aged 4 years or older with a confirmed diagnosis of NPC, a baseline SARA score of 7 to 34 points, and not receiving any other investigational therapies; patients were permitted to be receiving treatment with miglustat.

Patients were randomised in a 1:1 ratio to receive either levacetylleucine or placebo for 12 weeks in Period I. In Period II, patients switched to the opposite (either levacetylleucine or placebo) for 12 weeks. Patients aged ≥ 13 years received 4 g/day (as 2 g morning dose, 1 g afternoon dose and 1 g evening dose). The levacetylleucine dose in children under 13 years was based on patient's body weight (see section 4.2).

A total of 60 patients were randomised and treated, and 59 (98%) completed both treatment periods with levacetylleucine and placebo.

Of the 60 randomised patients (37 adults and 23 paediatric patients), 27 were female and 33 were male. The median age at treatment initiation was 25 years (range: 5 to 67 years). 90% of the patients were White, 3% Asian and 7% Other. In total, 51 (85%) patients received miglustat treatment prior to randomisation and during the study.

The primary endpoint measure was the measurement of neurological signs, symptoms and functioning as measured by the Scale for the Assessment and Rating of Ataxia (SARA).

The SARA assessment was carried out at baseline and then assessed at the end of Period I (Week 12) and the end of Period II (Week 24). Treatment with levacetylleucine demonstrated a statistically significant difference in favour of levacetylleucine as compared to placebo on SARA (Table 3).

Table 3. Summary of scale for the assessment and rating of ataxia (SARA) efficacy results*

Effect/Variable	Mean difference (SD)	Estimate (SE)	95% CI	p-value**
Baseline value	--	0.95 (0.04)	(0.86, 1.04)	< 0.001
Treatment effect (levacetylleucine versus placebo)	--	-1.28 (0.31)	(-1.91, -0.65)	< 0.001
Levacetylleucine total change versus baseline	-1.97 (2.43)	--	--	--
Placebo total change versus baseline	-0.60 (2.39)	--	--	--

CI = confidence interval; SD = standard deviation; SE = standard error.
* The change from baseline was assessed at the end of Period 1 (Week 12) and the end of Period 2 (Week 24).
** Two-sided p-value

The 30 patients receiving placebo in Period I had no meaningful change in the mean SARA score of -0.60 compared to those on levacetylleucine, who had a substantial change of -1.93. The remaining 30 patients who received levacetylleucine in Period I followed by placebo in Period II experienced significant worsening of symptoms on placebo, which effectively served as a washout from levacetylleucine (difference in mean SARA score between the end of Period I [Week 12] and the end of Period II [Week 24] of +1.55), reflecting a deterioration in neurological signs and symptoms when treatment with levacetylleucine was stopped (Figure 1).

In total, 9 patients (15%) were not on miglustat prior to randomisation and during the study. In these patients, there was also a change in the mean SARA score on levacetylleucine of -2.06.

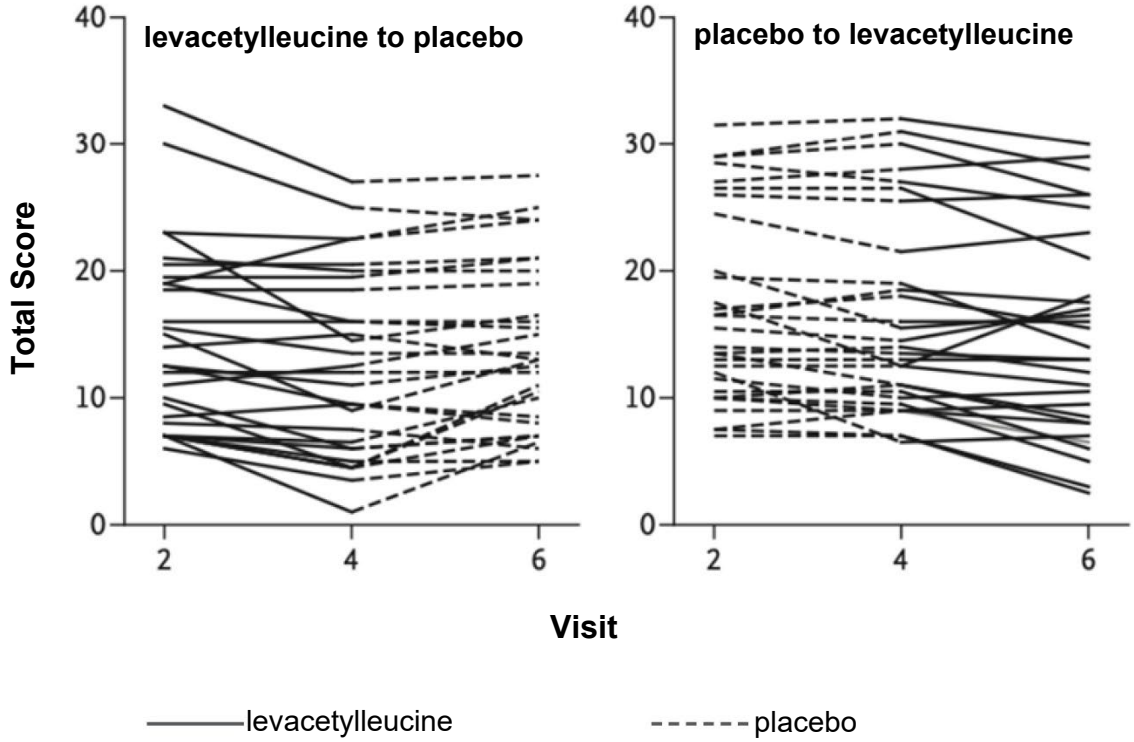

Figure 1. Individual patient SARA total scores at baseline, end of Period I, and End of Period II

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with levacetylleucine in one or more subsets of the paediatric population in the treatment of Niemann-Pick disease, type C (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration, levacetylleucine is rapidly absorbed. Median time to maximum concentration (C_{max}), t_{max}, is 1 hour (ranging from 0.5 to 2.5 hours). Mean, dose-normalised (per gram of levacetylleucine) C_{max} and area under the curve from time 0 to 24 hours ($AUC_{0-24hrs}$) were 4 mcg/mL/g and 9 h*mcg/mL/g. The absolute oral bioavailability is unknown.

No studies on food effect on absorption have been conducted.

Distribution

The mean (standard deviation [SD]) volume of distribution at steady state (V_{ss}) was 253 (125) L. Levacetylleucine is taken up by ubiquitously expressed monocarboxylate transporters, thereby delivering levacetylleucine to all tissues including the central nervous system.

Elimination

The mean (SD) clearance is 139 (59) L/h. The estimated half-life is around 1 hour. No or only minor accumulation was observed after repeat administration.

Characteristics in specific groups of subjects or patients

There were no clinically significant differences in the PK of levacetylleucine based on age (range: 6-67 years), sex, race/ethnicity or body weight (range: 20.5-98.4 kg).

Renal or hepatic impairment
The effect of renal or hepatic impairment on the PK of levacetylleucine has not been studied.

Interaction with other medicinal products

In vitro studies showed that levacetylleucine, at therapeutic concentrations, does not significantly inhibit the enzyme activity of cytochrome P450 (CYP450) isoforms. Levacetylleucine does not have induction potential towards CYP450 enzymes.

In vitro, levacetylleucine inhibited the efflux transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) or bile salt export pump (BSEP) (see section 4.5).

Levacetylleucine is a substrate and an *in vitro* inhibitor of organic anion transporter (OAT)1 and OAT3. The likelihood of clinically meaningful drug interactions is considered low.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

No effect on fertility was seen in rats at doses up to 1 000 mg/kg/day (1.5- to 2.3-fold human exposure). In embryofoetal development studies, levacetylleucine did not induce adverse developmental effects at doses up to 1 000 mg/kg/day in rats (2.0-fold human exposure). In rabbits,

external and skeletal malformations were observed at 1 250 mg/kg/day (7.1-fold of human exposure) with a no observed adverse effect level of 675 mg/kg/day (4.9-fold human exposure). No adverse effects were observed in a pre- and postnatal development study in rats at doses up to 1 000 mg/kg/day.

Carcinogenesis

No carcinogenicity studies have been conducted. The carcinogenic risk is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isomalt (E953)
Hypromellose
Strawberry flavour (contains propylene glycol (E1520))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aqneursa is supplied in single-dose paper-backed aluminium/polyethylene sachets.

Pack sizes:

- 28 single-dose sachets
- multipack containing 112 (4 packs of 28) single-dose sachets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Appearance of Aqneursa after reconstitution is an aqueous suspension, fluid, homogeneous, white, cloudy of fine particles without agglomeration.

Further information on administration through gastrostomy tube (French size 18 or larger)

- The enteral feeding should be stopped if the patient is on continuous feeding.
- At least 20 mL of water should be drawn into a catheter tip syringe and the tube should be flushed to prevent interactions between enteral feed and Aqneursa.
- The entire suspension with the required dose prepared according to section 4.2 should be drawn into the catheter tip syringe.

- The suspension should be given into the gastrostomy tube immediately (within 30 minutes) by applying steady pressure.
- The catheter tip syringe should be refilled with at least 20 mL of water and the tube flushed.
- The feeding can be restarted when appropriate.

7. MARKETING AUTHORISATION HOLDER

IntraBio Ireland Ltd
10 Earlsfort Terrace
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/25/1928/001
EU/1/25/1928/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Sciensus International B.V.
Bijsterhuizen 31-42
6604 LV Wijchen
Netherlands

Patheon France
40 Boulevard De Champaret
38300 Bourgoin-Jallieu
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

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

- **Risk management plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON containing 28 sachets

1. NAME OF THE MEDICINAL PRODUCT

Aqneursa 1 g granules for oral suspension in sachet
levacetylleucine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 1 g levacetylleucine**.**

3. LIST OF EXCIPIENTS

Contains isomalt and propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

granules for oral suspension
28 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

IntraBio Ireland Ltd
10 Earlsfort Terrace
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1928/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aqneursa

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 OUTER PACKAGING

CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Aqneursa 1 g granules for oral suspension in sachet
levacetylleucine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 1 g levacetylleucine**.**

3. LIST OF EXCIPIENTS

Contains isomalt and propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

granules for oral suspension
Multipack: 112 (4 packs of 28) sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

IntraBio Ireland Ltd
10 Earlsfort Terrace
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1928/002 112 (4 packs of 28) sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aqneursa

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 OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Aqneursa 1 g granules for oral suspension in sachet
levacetylleucine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 1 g levacetylleucine.

3. LIST OF EXCIPIENTS

Contains isomalt and propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

granules for oral suspension
28 sachets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

IntraBio Ireland Ltd
10 Earlsfort Terrace
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aqneursa

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Aqneursa 1 g granules for oral suspension in sachet
levacetylleucine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 1 g levacetylleucine**.**

3. LIST OF EXCIPIENTS

Contains isomalt and propylene glycol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

granules for oral suspension
1 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

IntraBio Ireland Ltd
10 Earlsfort Terrace
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Aqneursa 1 g granules for oral suspension in sachet
levacetylleucine

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

What is in this leaflet

1. What Aqneursa is and what it is used for

Aqneursa contains the active substance levacetylleucine, a modified amino acid.

Aqneursa is used in **adults and children aged 6 years and older and weighing at least 20 kg** to treat neurological symptoms of **Niemann-Pick type C** disease
- in combination with miglustat: another Niemann-Pick type C disease medicine, or
- on its own if miglustat is not tolerated.

In patients with this hereditary disease, specific changes in certain genes disrupt the function of lysosomes (small sacs inside the body's cells that digest large molecules, such as fats). The disruption causes increased amount of lipids, cholesterol and other fats stored in cells, which the body cannot break down. This leads to progressive loss of nerve cells with symptoms that include movement coordination problems, slurred speech, difficulty swallowing and uncontrollable shaking. Levacetylleucine improves function of lysosomes, thereby reducing the amount of fats and cholesterol in cells.

2. What you need to know before you take Aqneursa

Do not take Aqneursa
- if you are allergic to levacetylleucine or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
This medicine may cause allergic reactions, including sudden and severe allergic reactions. Stop taking Aqneursa and immediately talk to a doctor if you have allergic reactions after taking Aqneursa. Symptoms of include:
- breathing difficulties
- swelling of the face, lips, throat or tongue
- itchy rash on one part or the whole body

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

Aqneursa may affect how other medicines work or may make their side effects more likely. In particular, tell your doctor especially if you take any of the following medicines:
- digoxin: to treat heart weakness and irregular heartbeat
- dabigatran: to inhibit blood clotting
- loperamide: to treat diarrhoea
- irinotecan, doxorubicin, vinblastine, paclitaxel, seliciclib: to treat cancer
- fexofenadine: to treat symptoms of an allergy
- quinidine: to treat heart rhythm disorders
- talinolol: to lower blood pressure
- sulfasalazine: to treat severe bowel and rheumatic joint inflammation
- rosuvastatin: to lower elevated cholesterol levels

Other medicines may affect how Aqneursa works. In particular, tell your doctor if you are taking the following medicines:
- N-acetyl-DL-leucine, N-acetyl-D-leucine: to treat acute vertigo

Children and adolescents
Aqneursa is not recommended for children aged less than 6 years or weighing less than 20 kg.

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

- **Pregnancy**
  Aqneursa is not recommended during pregnancy.

- **Women of childbearing potential**
  Women who are able to have a baby are recommended to use effective contraception during treatment with Aqneursa.

- **Breast-feeding**
  It is not known if levacetylleucine passes into breast milk. This medicine may harm your nursing baby.
  If you are breast-feeding, you and your doctor will need to decide whether to continue breast-feeding or Aqneursa therapy. This will take into account the benefits of breast-feeding for the baby and the benefits of Aqneursa for the nursing mother.

Driving and using machines
Aqneursa has no or negligible influence on the ability to drive and use machines.

Aqneursa contains isomalt and propylene glycol
Each sachet contains 642.2 mg isomalt. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains 0.153 mg propylene glycol in each sachet.

3. How to take Aqneursa

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

The recommended dose is based on patient's body weight in kilograms and taken as follows:

Patient's body weight	Morning dose	Afternoon dose	Evening dose
20 to 24 kg	1 sachet	No dose	1 sachet
25 to 34 kg	1 sachet	1 sachet	1 sachet
35 kg or more	2 sachets	1 sachet	1 sachet

Method of use
Avoid food and drink 30 minutes before and 2 hours after administration.

- **Oral use with liquid**
  - Pour the content of one sachet into 40 mL (3 tablespoons) of water. Stir until fully mixed. Do not use hot liquid.
  - Drink all of the mixture immediately after preparation (within 30 minutes).
  - If the medicine is not taken within 30 minutes of preparation, stir it again before drinking.
  - A small amount of mixture may remain after drinking; no additional rinsing should be done in this case.
  - Repeat all steps if a second sachet is required.

- **Use via gastrostomy tube**
  Aqneursa may also be given via a tube through the abdomen into the stomach (French size 18 or larger):
  - Stop the feeding via tube (if on continuous feeding).
  - Draw up at least 20 mL of water into a catheter tip syringe and flush the tube to prevent interactions between feed and Aqneursa.
  - Empty the content of one sachet into 40 mL of water.
  - Mix until all granules are evenly distributed in the liquid.
  - Draw up the entire mixture into the catheter tip syringe.
  - Administer the mixture into the gastrostomy tube immediately (within 30 minutes) by applying steady pressure. Do not keep the mixture for later use.
  - Repeat the steps listed above starting with emptying the sachet if a second sachet is required.
  - Refill the catheter tip syringe with at least 20 mL of water and flush the gastrostomy tube.
  - Restart the feed when appropriate.

If you take more Aqneursa than you should
Inform your doctor or pharmacist if this occurs.
Symptomatic treatment is recommended.

If you forget to take Aqneursa
Do not take a double dose to make up for a forgotten dose. Continue the next dose as scheduled.

If you stop taking Aqneursa
Do not stop treatment without approval of your doctor.

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.

Side effects may occur with following frequency:

Common, may affect up to 1 in 10 people
- wind (flatulence)

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 Aqneursa

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 sachet, carton and/or label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

What Aqneursa contains
- The active substance is levacetylleucine. One single-dose sachet contains 1 g levacetylleucine.
- The other excipients are isomalt (E953), hypromellose, strawberry flavour (contains propylene glycol (E1520)). See section 2 “Aqneursa contains isomalt and propylene glycol”.

What Aqneursa looks like and contents of the pack
Aqneursa granules for oral suspension are white to off-white, strawberry-flavoured granules.

Aqneursa is supplied in single-dose paper-backed aluminium/polyethylene sachets and packed in a carton.

Pack sizes:

- 28 single-dose sachets
- Multipack containing 112 (4 packs of 28) single-dose sachets

Not all pack sizes may be marketed.

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Ireland

Manufacturer
Sciensus International B.V.
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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.