EU Risk Management Plan for Aqneursa® (levacetylleucine)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 12 June 2023

Date of final sign-off: 30 July 2025

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission

Summary of significant changes in this RMP: Not applicable

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

QPPV name: Dr. Zurab Koberidze

QPPV signature: 

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	2(S)-(acetylamino)-4-methylpentanoic acid, otherwise known as N-acetyl-L-leucine (Proposed INN: levacetylleucine)
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	IntraBio Ireland Ltd
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Aqneursa®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: The active ingredient of Aqneursa is N-acetyl-L-leucine, an amino acid derivative resulting from N-acetylation of L-leucine
	Summary of mode of action: N-acetyl-L-leucine targets underlying neurological dysfunction caused by mutations in *NPC1* or *NPC2* genes. It enters the enzyme-controlled pathways that correct metabolic dysfunction, improve mitochondrial function/adenosine triphosphate (ATP) production, and improve lysosomal function. The benefits of enhancing mitochondrial and lysosomal health include reducing neuroinflammation and improving cellular function.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Aqneursa Product Information (PI)
Indication(s) in the EEA	Current: 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.
	Proposed (if applicable): Not applicable

<table>
<tr><td>Dosage in the EEA</td><td>Current:

<u>Posology</u>

The recommended dose is based on the patient’s body weight in kg according to Table 1.

Table 1: Recommended dose
<table>
<tr><th>Patient’s body weight</th><th>Morning dose</th><th>Afternoon dose</th><th>Evening dose</th></tr>
<tr><td>20 to 24 kg</td><td>1 g
(1 sachet)</td><td>No dose</td><td>1 g
(1 sachet)</td></tr>
<tr><td>25 to 34 kg</td><td>1 g
(1 sachet)</td><td>1 g
(1 sachet)</td><td>1 g
(1 sachet)</td></tr>
<tr><td>35 kg or more</td><td>2 g
(2 sachets)</td><td>1 g
(1 sachet)</td><td>1 g
(1 sachet)</td></tr>
</table></td></tr>
<tr><td></td><td>Proposed (if applicable): Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current (if applicable): Granules for oral suspension in sachet. Each sachet contains 1 g levacetylleucine.</td></tr>
<tr><td></td><td>Proposed (if applicable): Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

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.

Incidence and prevalence: NPC is a rare (orphan), genetic disease. The birth prevalence of NPC is estimated at 1 per 100,000 in the European Union (EU), with published birth prevalence rates in the EU ranging from 0.35 per 100,000 in the Netherlands [Poorthuis et al. 1999] to 2.2 per 100,000 in North Portugal [Pinto et al. 2004].

Demographics of the population in the proposed indication –age, gender, racial and/or ethnic origin and risk factors for the disease: The age at diagnosis ranges from infancy to older adult.

NPC is an autosomal-recessive genetic disorder caused by mutations in either the *NPC1* or *NPC2* genes that encode the NPC1 and NPC2 proteins [Millat et al. 2005]. NPC occurs in males and females and in all races and ethnicities [National Organization for Rare Disorders, Inc. NORD, 1986, last update 2023]. Globally, Acadians in Nova Scotia and a Bedouin group in Israel have a higher-than-average frequency due to a founder effect [Patterson 2000, last update 2020].

The main existing treatment options: No curative therapy exists for NPC. In the EU, Zavesca® (miglustat) is authorised for the treatment of progressive neurological manifestations in adult patients and paediatric patients with NPC. Miglustat has been shown to mildly slow the general progression of neurological symptoms in some patients [Patterson et al. 2015]. However, open-label or observational studies indicate that stabilization or even improvement of clinical condition is not maintained under miglustat treatment [Freihuber et al. 2023; Fecarotta et al. 2015; Patterson et al. 2020]. Notable side effects of miglustat are loose stools and excessive flatus, that may be managed with dietary modification (by reduction or removal of lactose and other sugars), and physiologic tremor [Patterson 2000, last update 2020].

Natural history of the indicated condition in the population, including mortality and morbidity: The clinical presentation of NPC disease is characterised by broad heterogeneity in serious and debilitating systemic, psychiatric, and neurological symptoms. These symptoms vary markedly depending on the age of onset of neurological symptoms, from a rapidly progressing neonatal form to an adult-onset chronic neurodegenerative condition.

Infantile and juvenile patients often experience the most severe symptoms, including epileptic seizures and cataplexy. The symptoms of NPC patients who survive infancy are dominated by progressive neurodegeneration of the brain [Patterson et al. 2013]. Adult patients experience severe cognitive impairment, dementia, and psychosis.

NPC is always fatal. The majority of NPC patients are children and die before the age of 20. Life expectancy varies from death in infancy to >60 years (dependent on age of onset) with a median age of death of around 13 years [Garver et al. 2007; Bianconi et al. 2019].

Important co-morbidities: None known.

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies with N-acetyl-L-leucine (company code: IB1001) and relevance to human usage are presented in Table SII.1.

Table SII.1. Key safety findings from non-clinical studies and relevance to human usage

Key safety findings from non-clinical studies	Relevance to human usage
Toxicity Key issues identified from acute or repeat-dose toxicity studies: In the initial 6-week, oral repeat-dose toxicity study in dogs [Study No. 36243], treatment with 750 or 2500 mg/kg/day N-acetyl-L-leucine led to signs of gastrointestinal intolerance in form of emesis, increased salivation, and defaecation (diarrhoea, partly greenish discoloured) shortly after the p.o. administration in dogs. Two hours after dosing these signs had resolved completely. No test item-related changes in any other parameter/endpoint were observed/measured. The no observed adverse effect level (NOAEL) in dogs was 2500 mg/kg/day (given p.o.). Two pivotal Good Laboratory Practice (GLP) repeat-dose toxicity studies with oral administration have been conducted: a 26-week study in rats [Study No. 36242] and a 39-week study in dogs [Study No. 8422660]. In these chronic toxicity studies in rats and dogs, N-acetyl-L-leucine was well tolerated. No mortality and no relevant findings beside liquid faeces being considered non-adverse were observed up to doses of 800 mg/kg/day in dogs. In rats, adverse test item-related effects were noted only at the 2500 mg/kg/day level. Adverse effects consisted of decreased body weight (males only), changes of clinical chemistry parameters (males and females), changes of urine parameters (females only), increased kidney weights (males and females), and histopathological changes (increased incidence and severity of tubular basophilia and/or hyaline tubular casts in the kidney; males only, which are potentially related to alpha 2-microglobulin expression, which is specific for male rats and not relevant for humans).	None
Reproductive/developmental toxicity: No changes to the full panel of reproductive organ tissues were observed in any non-clinical toxicology studies, including GLP-compliant, 26-week and 39-week repeat-dose toxicity studies in rats and dogs. A dedicated fertility study in rats is ongoing. Embryofoetal developmental toxicity studies were conducted in rats [Study No. 8519317] and rabbits [Study No. 8519173]. In rats no maternal or embryofoetal toxicities were observed up to the highest tested dose of 1000 mg/kg/day. Pregnant New	Considering the embryofoetal toxicities observed in rabbits, a respective human risk cannot be excluded. Respective studies to further elucidate/disconfirm a potential embryo-foetal

Zealand white rabbits were administered 675, 1250, or 2500 mg/kg/day N-acetyl-L-leucine once daily via oral gavage. Due to foetal malformations in the group administered 2500 mg/kg/day, the high-dose level was decreased to 1925 mg/kg/day for the 14 remaining animals. N-acetyl-L-leucine-related effects in maternal animals were limited to decreased food consumption at all dose levels examined and clinical observations of soft faeces, brown discolouration of the hair in the urogenital region, and thin appearance in the group administered 2500/1925 mg/kg/day. Developmental toxicity observed in the groups administered ≥1250 mg/kg/day included decreased foetal body weight and foetal external malformations of open/partially open eye and hyperflexion of the limbs. In the group administered 2500/1925 mg/kg/day, skeletal malformations included misshapen maxilla, premaxilla, and frontal bones. Thus, based on effects on food consumption and developmental toxicity in groups administered ≥1250 mg/kg/day, the maternal and developmental NOAEL is 675 mg/kg/day.	toxicity in rabbits are ongoing. The Summary of Product Characteristics (SmPC), Section 4.6, states that there are no data on the use of N-acetyl-L-leucine in pregnant women. Studies in animals have shown reproductive toxicity. Aqneursa is not recommended during pregnancy and in women of childbearing potential not using contraception.
Genotoxicity: A standard battery of in vitro (AMES and chromosome aberration test) and in vivo (micronucleus test) genotoxicity tests revealed no evidence of mutagenic or clastogenic potential.	None
Carcinogenicity: N-acetyl-L-leucine is not genotoxic and no changes indicative of a carcinogenic potential have been identified in chronic toxicity studies. In addition, no carcinogenic potential of N-acetyl-L-leucine is expected due to its chemical nature and mode of action. No dedicated carcinogenicity studies have been conducted. Given the nature of the molecule and absence of findings indicative for carcinogenic potential in chronic toxicity studies, carcinogenetic potential of N-acetyl-L-leucine is considered low.	N-acetyl-L-leucine is not genotoxic and available non-clinical and clinical data do not indicate a genotoxic/carcinogenic risk. However, no carcinogenicity studies have been completed. The carcinogenic risk is unknown. Carcinogenicity will be evaluated in a planned rasH2 mouse carcinogenicity study.
Phototoxicity: N-acetyl-L-leucine does not absorb light at 240 to 700 nm [Module 3.2.P.5.2]. Consequently, N-acetyl-L-leucine has no phototoxic potential.	None
Juvenile toxicity The tolerability and the dose-range finding for a juvenile toxicity study with N-acetyl-L-leucine in juvenile male and female Wistar rats was investigated [Study No. 8519168] with once daily oral gavage dosing of up to 1000 mg/kg/day from post-natal day (PND) 7 to PND28. Results indicated no test article-related mortality or clinical signs, and other observed findings were considered incidental and not related to treatment. No clear test	None

article-related alterations in body weight or body weight gain and food consumption were noted for animals administered up to 1000 mg/kg/day. Macroscopic examinations at necropsy on PND 29 showed no test article-related effects in male or female juvenile animals.	
Safety pharmacology and other toxicity-related information or data The effect of N-acetyl-L-leucine on central nervous system (CNS), cardiovascular (CV), and respiratory functions has been tested in GLP-compliant in vitro and in vivo studies. Safety pharmacology studies revealed no effects of N-acetyl-L-leucine administration on CNS, CV, or respiratory function following oral administration [Module 2.6.2, Section 4].	None

Part II: Module SIII - Clinical trial exposure

Overall, across the indications NPC, GM2 gangliosidosis, and Ataxia-Telangiectasia (A-T), 132 individual patients have been exposed to at least one dose of Aqneursa (company code: IB1001):

- 84 individual patients were exposed in NPC studies (60 in Study IB1001-301 [Parent Study completed; Bremova-Ertl et al. 2024, Extension Phase ongoing] and 33 in Study IB1001-201 [Parent Study and Extension Phase completed; Bremova-Ertl et al. 2022], with 9 patients participating in both studies),
- 30 patients were exposed in the GM2 gangliosidosis (Tay-Sachs and Sandhoff disease) study (IB1001-202; completed; Martakis et al. 2023), and
- 18 patients have been exposed in the A-T study (IB1001-203; ongoing).

Available clinical trial exposure data, including duration of exposure (Table SIII.1) as well as number of patients exposed by age group and gender (Table SIII.2), by dose (Table SIII.3), and by race (Table SIII.4) from completed studies is provided below.

Table SIII.1: Duration of exposure – completed studies

Treatment duration [days]	**Patients with NPC (ISS – SAF) (N=84)**	**Patients with GM2 gangliosidosis (SAF) (N=30)**	**Patients with GM2 gangliosidosis (SAFe) (N=14)**
Mean (SD)	229.3(296.98)	58.8 (27.6)	584.7 (190.5)
Median	86.00	49.0	721.5
Min, Max	36.0, 938.0	16, 132	266, 754

ISS = integrated summary of safety; Max = maximum; Min = minimum; SAF = safety analysis set; SAFe = safety analysis set – Extension Phase.

The NPC ISS comprises the IB1001-201 Parent Study, IB1001-201 Extension Phase, and IB1001-301 Parent Study. A total of 9 patients participated in both IB1001-201 and IB1001-301 studies. For these patients, baseline data of

IB1001-201 study are used.

Source: ISS Table 2.7.4.1.5 (exposure of IB1001-301 Parent Study, IB1001-201 Parent Study and Extension Phase); Study IB1001-202 clinical study report (CSR) Tables 14.1.13 (exposure of Parent Study), 14.1.21 (exposure of Extension Phase).

Table SIII.2: Age group and gender – completed studies

Age group[a]	**Patients with NPC (ISS – SAF) (N=84)**		**Patients with GM2 gangliosidosis (SAF) (N=30)**	
	M	F	M	F
Children (4 to <12 years)	6	6	2	6
Adolescents (12-<18 years)	5	12	0	2
Adults (18 to <60 years)	20	29	9	11
Older adults (≥60 years)	3	3	0	0
Total	34	50	11	19

F = female; ISS = integrated summary of safety; M = male; SAF = safety analysis set.

a: Actual age range (min, max) at baseline: 5, 67 years.

The NPC ISS comprises the IB1001-201 Parent Study, IB1001-201 Extension Phase, and IB1001-301 Parent Study. A total of 9 patients participated in both IB1001-201 and IB1001-301 studies. For these patients, baseline data of IB1001-201 study are used.

Source: ISS Tables 2.7.4.2.1, 2.7.4.3.1, 2.7.4.4.1, 2.7.4.5.1; Study IB1001-202 CSR Listings 16.2.1.2 and 16.2.3.1.

Table SIII.3: Patients exposed to Aqneursa by dose – completed studies

Daily dose [g]	**Patients with NPC (ISS – SAF) (N=84)**	**Patients with GM2 gangliosidosis (SAF) (N= 30)**
2, n (%)	6 (7.14%)	3
3, n (%)	3 (3.57%)	4
4, n (%)	75 (89.29%)	23

ISS = integrated summary of safety; SAF = safety analysis set.

The NPC ISS comprises the IB1001-201 Parent Study, IB1001-201 Extension Phase, and IB1001-301 Parent Study. A total of 9 patients participated in both IB1001-201 and IB1001-301 studies.

For the ISS, the maximum daily dose is provided. For GM2 gangliosidosis, the dose in the IB1001-202 Parent Study is provided.

Source: ISS Table 2.7.4.1.5; Study IB1001-202 CSR Listing 16.2.4.2.

Table SIII.4: Patients exposed to Aqneursa by race – completed studies

Race	Patients with NPC (ISS – SAF) (N=84)	Patients with GM2 gangliosidosis (SAF) (N=30)
Asian, n (%)	2 (2.38)	1 (3.3)
White, n (%)	76 (90.48)	29 (96.7)
Other, n (%)	6 (7.14)	0

ISS = integrated summary of safety; SAF = safety analysis set.

The NPC ISS comprises the IB1001-201 Parent Study, IB1001-201 Extension Phase, and IB1001-301 Parent Study. A total of 9 patients participated in both IB1001-201 and IB1001-301 studies. For these patients, baseline data of IB1001-201 study are used. A total of 9 patients participated in both IB1001-201 and IB1001-301 studies. For these patients, baseline data of IB1001-201 study are used.

Source: ISS Table 3.7.4.1.1; Study IB1001-202 CSR Table 14.1.4.

Part II: Module SIV - Populations not studied in clinical trials

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

Important exclusion criteria in the pivotal Phase 3 study (Study IB1001-301 Parent Study) carried out in Europe are discussed below:

1. Patients who had any known hypersensitivity or history of hypersensitivity to:

a. Acetyl-Leucine (DL-, L-, D-) or derivatives;

b. Excipients of the IB1001 sachet (namely isomalt, hypromellose, and strawberry flavour);

c. Excipients of the placebo sachet (namely isomalt, hypromellose, strawberry flavour, citric acid, microcrystalline cellulose, lactose, and denatonium benzoate).

Reason for exclusion: Patients with known or suspected hypersensitivity to the active ingredient or the excipients are at greater risk of hypersensitivity reactions to Aqneursa.

Is it considered to be included as missing information?: No

Rationale: Hypersensitivity to the active substance or any of the excipients is a contraindication for use (SmPC, Section 4.3).

2. Simultaneous participation in another clinical study or participation in any clinical study involving administration of an investigational medicinal product (IMP) ("study drug") for at least 42 days prior to Visit 1. At the discretion of the Investigator, Medical Monitor, and Sponsor, the washout period for specific IMPs may be longer based on the pharmacological activity and pharmacokinetics (PK) of the drug.

Reason for exclusion: Patients who are participating in or who have recently participated in another clinical trial are routinely excluded from clinical trials to avoid confounding factors affecting safety and efficacy.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid confounding factors affecting efficacy assessments and not because of a particular safety concern.

3. Patients with a physical or psychiatric condition which, at the Investigator's discretion and in consultation with the Medical Monitor and Sponsor (as applicable), could put the patient at risk, confound the study results, or interfere with the patient's participation in the clinical study, (i.e., reliably perform study assessments).

Reason for exclusion: Patients with relevant co-morbidities could have been excluded if their participation would have put the patient at risk, confounded study results, or interfered with the patient's participation in the clinical study.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid confounding factors affecting efficacy assessments (functional tests) and not because of a particular safety concern.

4. Known or persistent use, misuse, or dependency of medication, drugs, or alcohol.

Reason for exclusion: Patients with persistent use, misuse, or dependency on medication, drugs, or alcohol, could have been excluded if their participation would have put the patient at risk, confounded study results, or interfered with the patient's participation in the clinical study.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid confounding factors affecting efficacy assessments (functional tests) and not because of a particular safety concern.

5. Current or planned pregnancy or women who were breastfeeding.

Reason for exclusion: as a precautionary measure, pregnant and breastfeeding are routinely excluded from clinical trials.

Is it considered to be included as missing information?: No

Rationale: Developmental toxicity is included as an important potential risk in the RMP to be reassessed once the results of the developmental toxicity studies are available.

The SmPC, Section 4.6, states that there are no data from the use of N-acetyl-L-leucine in pregnant women. Studies in animals have shown reproductive toxicity. Aqneursa is not recommended during pregnancy and in women of childbearing potential not using contraception.

6. Patients with severe vision or hearing impairment (that is not corrected by glasses or hearing aids) that, at the Investigator's discretion, interfered with their ability to perform study assessments.

Reason for exclusion: Uncorrected severe vision or hearing impairment may have impacted the patient's ability to perform the study assessments.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid confounding factors affecting efficacy assessments (functional tests) and not because of a particular safety concern.

7. Patients who had been diagnosed with arthritis or other musculoskeletal disorders affecting joints, muscles, ligaments, and/or nerves that by themselves affect patient's mobility and, at the Investigator's discretion, interfered with their ability to perform study assessments.

Reason for exclusion: The presence of arthritis or other musculoskeletal disorders may have impacted the patient's ability to perform the study assessments (functional tests).

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid confounding factors affecting efficacy assessments (functional tests) and not because of a particular safety concern.

8. Patients unwilling and/or who were not able to undergo a 42-day washout period from any of the following prohibited medication prior to Visit 1 (Baseline 1) and remain without prohibited medication through Visit 6:

a. N-Acetyl-DL-Leucine (e.g., Tanganil®);

b. N-Acetyl-L-Leucine (prohibited if not provided as IMP in the IB1001-301 study);

c. Sulfasalazine;

d. Rosuvastatin.

Reason for exclusion: Pharmacology studies indicate that N-acetyl-D-leucine competes with N-acetyl-L-leucine for uptake by the monocarboxylate transporters (MCTs) [Module 2.6.2, Section 2.1.1]. Concomitant use of N-acetyl-L-leucine with N-acetyl-DL-leucine and N-acetyl-D-leucine should be avoided (SmPC, Section 4.5).

N-acetyl-L-leucine may be an inhibitor of breast cancer resistance protein (BCRP) [Module 2.6.4, Section 7.3]. A potential interaction of N-acetyl-L-leucine with other medicinal products that are substrates of BCRP (e.g. sulfasalazine, rosuvastatin) cannot be excluded (SmPC, Section 4.5).

Is it considered to be included as missing information?: No

Rationale: The potential interactions described above are addressed in the SmPC, Section 4.5.

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

Limitations of the clinical development program for Aqneursa should be considered in the context of the long-term use of the racemate of the active substance, N-acetyl-DL-leucine (Tanganil®), which has been marketed in France as an oral treatment for acute vertigo since the 1950s.

The clinical development programme for Aqneursa is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

Long-term safety and tolerability of Aqneursa was investigated in a 2-year Extension Phase of the Phase 2 study (N=19). The duration of exposure during Treatment period I plus Treatment period II ranged from 176 days (25.1 weeks) to 816 days (116.6 weeks) [IB1001-201 CSR, Section 12.1].

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

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program for Aqneursa.
Breastfeeding women	
Patients with relevant co-morbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients	Not included in the clinical development program for Aqneursa.
Patients with a disease severity different from inclusion criteria in clinical trials	Asymptomatic patients were not included in the clinical development program for Aqneursa. To ensure that patients were able to participate in functional testing (efficacy readouts), entry to clinical studies was restricted to patients who were able to walk, at the least, short distances, with or without support, or who were able to perform the 9-hole peg test of the dominant hand (9HPT-D) (time limit = 150 seconds).
Population with relevant different ethnic origin	The majority of patients were White (see Table SIII.4).
Subpopulations carrying relevant genetic polymorphisms	None known.
Other	Not applicable.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable. As of the data lock point for this RMP, Aqneursa was not authorised for sale in any country worldwide.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The basic active moiety of N-acetyl-L-leucine is a simple modified amino acid, and, therefore, the structure-activity of N-acetyl-L-leucine does not suggest abuse potential. N-acetyl-L-leucine is

metabolized via deacetylation (cleavage of the acetic bond acetyl-group, releasing acetate) giving rise to a single metabolite, L-leucine. L-leucine is a naturally occurring amino acid that is endogenously present in humans (as is acetate) and human diets. In addition, no signs indicative of a withdrawal effect have been reported / observed during recovery periods in non-clinical safety studies, nor were clinical signs indicative of abuse potential observed during non-clinical or clinical studies with N-acetyl-L-leucine, or from human data from the use of Tanganil®, which has been marketed in Europe for decades. Adverse events (AEs) were evaluated consistently throughout clinical studies by the data safety monitoring board (DSMB) for signs of abuse potential and no AEs have been determined to be related to abuse potential.

In Study IB1001-301, review of AEs matching the prespecified preferred terms (PTs) for abuse potential determined that these did not indicate abuse potential. In addition, all AEs were evaluated for potential abuse potential relatedness, but none were considered indicative of abuse potential [Study IB1001-301 interim CSR, Section 12.3.1.5].

Part II: Module SVII - Identified and potential risks

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

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse reactions for Aqneursa, all considered to be risks with minimal clinical impact on patients (in relation to the severity of the indication treated), are presented in Table SVII.1.1.1.

Table SVII.1.1.1 Adverse reactions for Aqneursa

System organ class	Frequency	Adverse reaction
Gastrointestinal disorder	Common	flatulence

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

Important Potential Risk: hepatotoxicity

Risk-benefit impact:

No treatment-emergent adverse events (TEAEs) of hepatobiliary disorders were reported in completed studies with IB1001 in NPC. However, liver enzyme value changes were observed in some patients; therefore, this potential risk cannot be excluded.

Important Potential Risk: carcinogenicity

Risk-benefit impact:

N-acetyl-L-leucine is not genotoxic and available non-clinical and clinical data do not indicate a genotoxic/carcinogenic risk. However, no carcinogenicity studies have been completed. The carcinogenic risk is unknown; therefore, this potential risk cannot be excluded.

Carcinogenicity will be evaluated in a planned rasH2 mouse carcinogenicity study.

Important Potential Risk: developmental toxicity

Risk-benefit impact:

There are no data on the use of IB1001 in pregnant women. However, an animal study in rabbits indicated reproductive toxicity; therefore, this potential risk cannot be excluded. Respective studies to further elucidate/disconfirm a potential embryo-foetal toxicity in rabbits are ongoing.

Missing information: Long-term safety

Risk-benefit impact:

NPC is a chronic disease requiring life-long treatment. In completed studies in NPC, patients have been treated for up to around 2.5 years. Longer-term safety in NPC patients is evaluated as part of the ongoing study, IB1001-301 Extension Phase, and as part of a non-interventional study using the existing International Niemann-Pick Disease Registry (INPDR) as data source.

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

Not applicable for initial marketing authorisation application.

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: hepatotoxicity

Potential mechanisms:

Not known.

Evidence source(s) and strength of evidence:

Non-clinical studies: No impacts on markers of hepatic function, as well as on liver histopathology, were observed in animal studies up to 6- / 9-months of daily dosing at exposures up to 20-fold of human exposure.

Clinical studies: Transient increases in liver enzymes were observed in individual patients treated with IB1001 in completed clinical studies in NPC; these were not associated with hepatobiliary disorders adverse events.

Characterisation of the risk:

Transient increases in liver enzymes were observed in individual patients treated with IB1001 in clinical studies.

IB1001-301 Parent Study

No TEAEs were reported in the hepatobiliary disorders system organ class (SOC) during the IB1001-301 Parent Study. No TEAEs related to abnormal liver function tests were reported during IB1001

treatment in the IB1001-301 Parent Study; the only subject with an abnormal liver function test (blood alkaline phosphatase increased) was in the placebo group (Table SVII.3.1).

Table SVII.3.1 TEAEs associated with hepatotoxicity

Preferred Term	**IB1001-301 (N=60)**		**IB1001-301 (N=59)**	
	n (%)	**M**	**n (%)**	**m**
Blood alkaline phosphatase decreased	0 (0%)	0	1 (1.7%)	1

N indicates the number of patients treated. m=number of events, n (%)=number (percentage) of patients. Adverse events are coded according to MedDRA, version 24.1.

IB1001-201 Parent Study and Extension Phase

No TEAEs were reported in the hepatobiliary disorders SOC during the IB1001-201.

One TEAE related to increased liver test values was reported. This patient reported a TEAE of Blood alkaline phosphatase increased (125 U/L at Visit 3) that was non-serious and mild in severity. No action was taken with the study drug and the TEAE had resolved while on study drug (89 U/L at Visit 4). The Blood alkaline phosphatase increased was considered by the investigator not to be related to study drug but rather to the patient's NPC.

Risk factors and risk groups:

None known.

Preventability:

Not known.

Impact on the risk-benefit balance of the product:

No TEAEs of hepatobiliary disorders were reported in completed studies with IB1001 in NPC. However, liver enzyme value changes were observed in some patients; therefore, this potential risk cannot be excluded.

Long-term safety in NPC patients is evaluated as part of the ongoing study, IB1001-301 Extension Phase and as part of a non-interventional study using the existing International Niemann-Pick Disease Registry (INPDR) as data source.

Public health impact:

None expected.

Important Potential Risk: carcinogenicity

Potential mechanisms:

Not known.

Evidence source(s) and strength of evidence:

IB1001 is not genotoxic and available non-clinical and clinical data do not indicate a genotoxic/carcinogenic risk. However, no carcinogenicity studies have been conducted and the carcinogenic risk is unknown.

Characterisation of the risk:

IB1001 is not genotoxic and available non-clinical data do not indicate a genotoxic/carcinogenic risk.

There were no treatment-emergent adverse events in the system organ class Neoplasms, benign, malignant and unspecified (including cysts and polyps) reported in studies with IB1001 (completed studies IB1001-201, IB1001-202, IB1001-301 Parent Study).

Risk factors and risk groups:

None known.

Preventability:

Not known.

Impact on the risk-benefit balance of the product:

N-acetyl-L-leucine is not genotoxic and available non-clinical and clinical data do not indicate a genotoxic/carcinogenic risk. However, no carcinogenicity studies have been completed. The carcinogenic risk is unknown; therefore, this potential risk cannot be excluded.

Carcinogenicity will be evaluated in a planned rasH2 mouse carcinogenicity study.

Public health impact:

None expected.

Important Potential Risk: developmental toxicity

Potential mechanisms:

Not known.

Evidence source(s) and strength of evidence:

In embryofoetal development studies, N-acetyl-L-leucine did not induce adverse developmental effects at doses up to 1000 mg/kg/day in rats (2.0-fold human exposure). In rabbits, external and skeletal malformations were observed at 1250 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 1000 mg/kg/day.

There are no data on the use of IB1001 in pregnant women.

Characterisation of the risk:

There are no data on the use of IB1001 in pregnant women.

Risk factors and risk groups:

None known.

Preventability:

Aqneursa is not recommended during pregnancy and in women of childbearing potential not using contraception (SmPC, Section 4.6; PIL, Section 2).

Impact on the risk-benefit balance of the product:

There are no data on the use of IB1001 in pregnant women. However, an animal study in rabbits indicated reproductive toxicity; therefore, this potential risk cannot be excluded. Respective studies to further elucidate/disconfirm a potential embryo-foetal toxicity in rabbits are ongoing.

Public health impact:

None expected.

SVII.3.2. Presentation of the missing information

Missing information: Long-term safety

Evidence source:

NPC is a chronic disease requiring life-long treatment. In completed studies in NPC, patients have been treated for up to around 2.5 years.

Long-term safety in NPC patients is evaluated as part of the ongoing study, IB1001-301 Extension Phase.

Long-term safety data related to Aqneursa will be evaluated as part of a non-interventional study using the existing International Niemann-Pick Disease Registry (INPDR) as data source.

Safety data will also be collected as part of routine pharmacovigilance post-approval.

Population in need of further characterisation:

NPC patients with long-term use of IB1001.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity; Carcinogenicity; Developmental toxicity
Missing information	Long-term safety

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none

III.2 Additional pharmacovigilance activities

IB1001-301 Extension Phase summary

Study short name and title:

IB1001-301 Extension Phase.

Rationale and study objectives:

Evaluate long-term safety and tolerability in patients with NPC.

Study design:

Open-label, safety, PK, and activity study in adults and children from birth with NPC, with rich PK sampling in children from 4 years to contribute to modelling of PK in children from birth to less than 4 years. In the Extension Phase, patients will receive IB1001 over three approximately one-year treatment periods (for a total of 3 years of treatment).

Safety assessments (including vital signs, blood and urine laboratory tests, adverse events) are done at 6-monthly visits.

Study population:

Enrolment is possible by two pathways:

- Pathway 1: patients with NPC aged from 4 years who participated in the IB1001-301 Parent Study
- Pathway 2: patients with NPC aged from birth enrolled directly into IB1001-301 Extension Phase

Milestones:

An updated protocol will be provided within 3 months of marketing authorisation.

Final report: 31 March 2029

Post-authorisation, non-interventional study using existing International Niemann Pick Disease Registry (INPDR) as data source

Study short name and title:

Post-authorisation, non-interventional study using existing International Niemann Pick Disease Registry (INPDR) as data source

Rationale and study objectives:

Evaluate long-term safety and tolerability of Aqneursa in patients with NPC.

Study design:

A non-interventional, multi-centre post-authorisation registry-based safety study performed in collaboration with the INPDR designed to collect long-term safety data and data on hepatic events in patients treated with N-acetyl-L-leucine.

Study population:

Patients with NPC enrolled in the INPDR and exposed to N-acetyl-L-leucine.

Milestones:

The protocol will be provided within 3 months of marketing authorisation. The collaboration with INPDR is planned for 3 years post-authorisation. The final study report will be provided no later than one year after the last receipt of safety data from the INPDR.

IB1001: A 26-Week Oral (Gavage) Administration Carcinogenicity Study in the Transgenic rasH2 Mouse

Study short name and title:

26-Week Oral (Gavage) Administration Carcinogenicity Study in the Transgenic rasH2 Mouse

Rationale and study objectives:

The objective of the study is to evaluate the carcinogenic potential of IB1001, when administered daily by oral gavage to 001178-T (hemizygous) rasH2 mice for at least 26 weeks.

Study design:

Pivotal, 26-week carcinogenicity study with IB1001 in 001178-T (hemizygous) rasH2 mice. IB1001 will be administered at the dose levels of 0 (control), 1000 (low), 2000 (intermediate), and 4000 (high) mg/kg/day. The study will also include a positive control.

Study population:

001178-T (hemizygous) rasH2 mice

Milestones:

Final report: 30 June 2027

IB1001: Intravenous (Slow Bolus) Preliminary Study of Embryo-Foetal Development in the Rabbit

Study short name and title:

Intravenous (Slow Bolus) Preliminary Study of Embryo-Foetal Development in the Rabbit

Rationale and study objectives:

The objective of the study is to determine the effects of the test article, IB1001, on the embryo-foetal survival and development of the rabbit, when administered once daily intravenously (slow bolus) from Gestation Days 7 to 20, inclusive, and then maintained undosed to Gestation Day 29. The toxicokinetic profile of the test article will also be assessed.

Study design:

Rabbits are administered intravenous (slow bolus) 250 or 300 mg/kg/day IB1001 or control once-daily from Gestation Days 7 to 20, inclusive, and then maintained undosed to Gestation Day 29.

Study population:

New Zealand White rabbit

Milestones:

Final report: 31 October 2025

IB1001: 8 Week Once Daily Oral (Gavage) Administration Dose Juvenile Toxicity Study in the Rat, Followed by a 4-Week Recovery Period

Study short name and title:

8 Week Once Daily Oral (Gavage) Administration Dose Juvenile Toxicity Study with IB1001 in the Rat

Rationale and study objectives:

The objective of the study is to assess the toxicity and toxicokinetic profile of IB1001, following once daily oral (gavage) administration to the juvenile rat from PND 7, for at least 8 weeks, followed by a 4-week recovery period. The purpose of this study is to provide data to support inclusion of paediatric patients in clinical trials.

Study design:

Once-daily oral gavage administration of 300, 600, or 1000 mg/kg/day IB1001 to juvenile male and female rats, from PND 7 to 28.

Study population:

Wistar Han rat

Milestones:

Final report: 31 December 2025

III.3 Summary Table of additional pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
IB1001-301 Extension Phase On-going	Evaluate long-term safety and tolerability in patients with NPC	Hepatotoxicity Long-term safety	Updated study protocol	3 months after marketing authorisation

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Final report	31 March 2029
Post-authorisation, non-interventional study using existing International Niemann Pick Disease Registry (INPDR) as data source Planned	Evaluate long-term safety and tolerability in patients with NPC	Hepatotoxicity Long-term safety	Study protocol	3 months after marketing authorisation
			Final report	To be confirmed
26-Week Oral (Gavage) Administration Carcinogenicity Study in the Transgenic rasH2 Mouse Planned	Evaluate the carcinogenic potential of IB1001	Carcinogenicity	Final report	30 June 2027
Intravenous (Slow Bolus) Preliminary Study of Embryo-Foetal Development in the Rabbit On-going	Study the effect of intravenous IB1001 on embryo-foetal development in the rabbit	Developmental toxicity	Final report	31 October 2025
8 Week Once Daily Oral (Gavage) Administration Dose Juvenile Toxicity Study with IB1001 in the Rat On-going	Assess the toxicity and toxicokinetic profile of IB1001 in juvenile rats	Developmental toxicity	Final report	31 December 2025

Part IV: Plans for post-authorisation efficacy studies

Not applicable. There are no planned post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hepatotoxicity	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Carcinogenicity	Routine risk communication: SmPC, Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Developmental toxicity	Routine risk communication: SmPC, Sections 4.6, 5.3; PIL, Section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Long-term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information:

	Legal status: prescription only medicine

V.2. Additional Risk Minimisation 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 minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: IB1001-301 Extension Phase, due 31 March 2029 Post-authorisation, non-interventional study using existing International Niemann Pick Disease Registry (INPDR) as data source
Carcinogenicity	Routine risk minimisation measures: SmPC, Section 5.3 Prescription only medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: 26-Week Oral (Gavage) Administration Carcinogenicity Study in the Transgenic rasH2 Mouse, due 30 June 2027
Developmental toxicity	Routine risk minimisation measures: SmPC, Sections 4.6, 5.3; PIL, Section 2. Prescription only medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: Intravenous (Slow Bolus) Preliminary Study of Embryo-Foetal Development in the Rabbit, due 31 October 2025 8 Week Once Daily Oral (Gavage) Administration Dose Juvenile Toxicity Study with IB1001 in the Rat, due 31 December 2025
Long-term safety	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: IB1001-301 Extension Phase, due 31 March 2029 Post-authorisation, non-interventional study using existing International Niemann Pick Disease Registry (INPDR) as data source

Part VI: Summary of the risk management plan

Summary of risk management plan for Aqneursa® (levacetylleucine)

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

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

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

I. The medicine and what it is used for

Aqneursa is authorised 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 (see SmPC for the full indication). It contains levacetylleucine as the active substance and it is administered orally.

Further information about the evaluation of Aqneursa’s benefits can be found in Aqneursa’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Aqneursa, together with measures to minimise such risks and the proposed studies for learning more about Aqneursa'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 package leaflet 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 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 Aqneursa is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Aqneursa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Aqneursa. 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 (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Hepatotoxicity; Carcinogenicity; Developmental toxicity
Missing information	Long-term safety

II.B Summary of important risks

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Non-clinical studies: No impacts on markers of hepatic function, as well as on liver histopathology, were observed in animal studies up to 6- / 9-months of daily dosing at exposures up to 20-fold of human exposure. Clinical studies: Transient increases in liver enzymes were observed in individual patients treated with IB1001 in completed clinical studies in NPC; these were not associated with hepatobiliary disorders adverse events.
Risk factors and risk groups	None known.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: IB1001-301 Extension Phase Post-authorisation, non-interventional study using existing International Niemann Pick Disease Registry (INPDR) as data source See section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Carcinogenicity	
Evidence for linking the risk to the medicine	IB1001 is not genotoxic and available non-clinical and clinical data do not indicate a genotoxic/carcinogenic risk. However, no carcinogenicity studies have been conducted and the carcinogenic risk is unknown.
Risk factors and risk groups	None known.
Risk minimisation measures	Routine risk minimisation measures: SmPC, Section 5.3 Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 26-Week Oral (Gavage) Administration Carcinogenicity Study in the Transgenic rasH2 Mouse See section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Developmental toxicity	
Evidence for linking the risk to the medicine	In embryofoetal development studies, N-acetyl-L-leucine did not induce adverse developmental effects at doses up to 1000 mg/kg/day in rats (2.0-fold human exposure). In rabbits, external and skeletal malformations were observed at 1250 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 1000 mg/kg/day. There are no data on the use of IB1001 in pregnant women.
Risk factors and risk groups	None known.
Risk minimisation measures	Routine risk minimisation measures: SmPC, Sections 4.6, 5.3; PIL, Section 2. Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Intravenous (Slow Bolus) Preliminary Study of Embryo-Foetal Development in the Rabbit 8 Week Once Daily Oral (Gavage) Administration Dose Juvenile Toxicity Study with IB1001 in the Rat

	See section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: IB1001-301 Extension Phase Post-authorisation, non-interventional study using existing International Niemann Pick Disease Registry (INPDR) as data source See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Aqneursa.

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

Study short name: IB1001-301 Extension Phase

Purpose of the study: Evaluate long-term safety and tolerability in patients with NPC

Study short name: Post-authorisation, non-interventional study using existing International Niemann Pick Disease Registry (INPDR) as data source

Purpose of the study: Evaluate long-term safety and tolerability in patients with NPC

Study short name: 26-Week Oral (Gavage) Administration Carcinogenicity Study in the Transgenic rasH2 Mouse

Purpose of the study: Evaluate the carcinogenic potential of IB1001

Study short name: Intravenous (Slow Bolus) Preliminary Study of Embryo-Foetal Development in the Rabbit

Purpose of the study: Study the effect of intravenous IB1001 on embryo-foetal development in the rabbit

Study short name: 8 Week Once Daily Oral (Gavage) Administration Dose Juvenile Toxicity Study with IB1001 in the Rat

Purpose of the study: Assess the toxicity and toxicokinetic profile of IB1001 in juvenile rats

Part VII: Annexes

Table of Contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.