31 May 2018
EMA/413721/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nityr

International non-proprietary name: nitisinone

Procedure No. EMEA/H/C/004582/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Ae,t	Cumulative amount of unchanged drug excreted into the urine until time t
Ae∞	Cumulative amount of unchanged drug excreted into the urine in infinite time
Ae-INF	Cumulative amount of unchanged drug excreted into the urine in infinite time
AeT	Cumulative amount of unchanged drug excreted into the urine until time T
ANCOVA	analysis of covariance
ANOVA	Analysis of variance
AUC∞	Area under the concentration-time curve from time zero to infinity
AUCt	Area under the concentration-time curve calculated to the last observable concentration at time t.
AUCτ	Area under the concentration-time curve during a dosage interval (τ) at steady-state
AUEC	Area under the effect-time curve
AUMC	Area under the moment curve, ie, the curve of the product of concentration and time vs time, from zero to infinity
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CL	Total body clearance of drug from the plasma
CL/F	Apparent clearance of drug from plasma after extravascular administration
CLcr	Creatinine clearance
CLr	Renal clearance of drug from the plasma
Cmax	Peak (maximum) plasma concentration of the drug
Cn,max	Maximum (peak) plasma drug concentration after regular administration of n doses
Cn,min	Minimum (trough) plasma drug concentration after regular administration of n doses
Css	Steady-state drug concentration in the plasma during constant-rate infusion
Css,av	Average steady-state drug concentration in the plasma during a dosage interval
Css,max	Maximum (peak) steady-state drug concentration in the plasma during a dosage interval
Css,min	Minimum (trough) steady-state drug concentration in the plasma during a dosage interval
Ct	Concentration of drug in the plasma at any time t.
CV	coefficient of variation

CYP1A2	Cytochrome P450 1A2
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
D	Dose
EC50	Concentration of drug producing 50% of Emax
Emax	Maximum effect a drug produces
Et or Ec	Extent of effect a drug produces at time t or at concentration c
EU	European Union
F	Absolute bioavailability
fe	Fraction of the systemically available drug excreted into the urine
Fr	Relative bioavailability
FT	Fourrier Transform
fu	Unbound fraction of drug in plasma
GC	Gas Chromatography
GLS	Geometric least square
HDPE	High-Density Polyethylene
HPLC	High performance liquid chromatography
HPPD	Hydroxy phenylpyruvate dioxygenase
HT-1	Hereditary tyrosinaemia type 1
IC50	Concentration of drug producing 50% inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
ka	Absorption rate constant (first-order)
KF	Karl Fischer titration
LC/MS/MS	Liquid chromatography with mass spectrometric identification and detection
MRT	Mean residence time
NMR	Nuclear Magnetic Resonance
pH	Negative of the logarithm of the hydronium ion activity
Ph. Eur.	European Pharmacopoeia

pKa	Ionisation constant
PP	Polypropylene
Rac(AUC)	Accumulation ratio based on AUC
Rac(Cmax)	Accumulation ratio based on Cmax
Rac(Cmin)	Accumulation ratio based on Cmin
SGF	Simulated Gastric Fluid
t	Student t; specify α level, df, 1-tailed or 2-tailed
tlag	Lag time for absorption
tmax	Time to peak (maximum) plasma concentration
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
V	Apparent volume of distribution in the 1-compartment model (V= Vz= Vss)
Vss	Volume of distribution at steady-state
Vss/F	Apparent volume of distribution at steady-state after extravascular administration
Vur	Volume of urine excreted
Vz	Apparent volume of distribution during the terminal (λz) phase
Vz/F	Apparent volume of distribution during the terminal (λz) phase after extravascular administration
XRPD	X-Ray Powder Diffraction
γ	Hill coefficient defining the steepness of the concentration-effect curve
λz	Apparent terminal-phase disposition rate constant (first-order)
τ	Dosage interval

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Cycle Pharmaceuticals Ltd submitted on 5 February 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Nityr, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2016.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of adult and paediatric (in any age range) patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Orfadin instead of non-clinical and clinical data, unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Orfadin 10 mg hard capsule
- Marketing authorisation holder: Swedish Orphan Biovitrum International AB
- Date of authorisation: 21-02-2005
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/04/303/003

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Orfadin 10 mg hard capsule
- Marketing authorisation holder: Swedish Orphan Biovitrum International AB
- Date of authorisation: 21-02-2005
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/04/303/003

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Orfadin 10 mg hard capsule
- Marketing authorisation holder: Swedish Orphan Biovitrum International AB
- Date of authorisation: 21-02-2005
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/04/303/003
- Bioavailability study number(s): CT-001 and CT-003

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Peter Kiely

- The application was received by the EMA on 5 February 2017.
- The procedure started on 23 February 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 May 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 May 2017.
- During the meeting on 22 June 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 6 December 2017.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 January 2018.
- During the PRAC meeting on 8 February 2018, the PRAC agreed on a PRAC Assessment Overview and

Advice to CHMP.

- During the CHMP meeting on 22 February 2018, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 26 February 2018.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 11 April 2018.
- During the CHMP meeting on 26 April 2018, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 30 April 2018.
- In a written procedure concluding on 14 May 2018, the Pharmacokinetics Working Party (PKWP) addressed the questions raised by the CHMP. The CHMP considered the views of the PKWP, as presented in the minutes of this meeting.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 16 May 2018.
- During the meeting on 31 May 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Nityr.

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation for Nityr tablets is submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended. The reference product is Orfadin, hard capsules (Swedish Orphan Biovitrum International AB), authorised in the EU since 21st February 2005 through the centralised procedure (EU/1/04/303/001-4).

Orfadin is indicated for treatment of adult and paediatric (in any age range) patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT 1) in combination with dietary restriction of tyrosine and phenylalanine.

The available treatment options for HT-1 prior to the use of nitisinone, included dietary restriction of phenylalanine and tyrosine and liver transplantation. However, diet alone does not prevent the progression of the disease. Disease management of HT-1 has significantly advanced since the introduction of nitisinone (NTBC). Nitisinone can rapidly normalise the biochemical markers of HT-1 and significantly improve the clinical symptoms in most patients. In the long term, it has markedly improved the life expectancy of HT-1 patients.

Nitisinone (2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, or NTBC) is an inhibitor of the 4-hydroxyphenyl-pyruvate dioxygenase (HDDP), an enzyme involved in the second step in tyrosine degradation. HPPD enzyme is located 'upstream' in the tyrosine degradation pathway with respect to the

enzyme fumarylacetoacetate hydrolase, the last step in tyrosine degradation which is deficient in patients suffering from HT-1. HPPD inhibition prevents the accumulation of maleylacetoacetate and fumarylacetoacetate, which occurs in HT-1 patients as a consequence of their inherited defect of fumarylacetoacetate hydroxylase activity.

They are partially converted to succinylacetone and succinylacetoacetate, which inhibit the porphobilinogen(PBG)-synthase activity in the heme synthesis pathway. This leads to accumulation and increased excretion in the urine of 5- aminolevulinate (5-ALA).

Nitisinone treatment leads to normalised porphyrin metabolism with normal erythrocyte porphobilinogen synthase activity and urine 5-ALA and decreased urinary excretion of succinylacetone.

Cycle Pharmaceutical initially proposed Nitisinone Cycle tablets in the doses of 2mg, 5mg and 10mg. The reference product ORFADIN capsules (EU/1/04/303/001-003) is available in 2mg, 5mg, 10mg and 20mg capsules, as well as in a 4mg/ml oral suspension for paediatric patients with difficulties swallowing.

Orfadin capsules and suspension are a nitisinone product approved by the Agency for HT-1. Due to thermal instability at room temperature, these products are required to be stored in a refrigerator for long term storage, which may be inconvenient for patients as a lifelong treatment. In light of this, Nityr, a room temperature stable formulation, may be a valuable option for patients.

Orphan designation has not been applied for this generic medicinal product. The reference product Orfadin 2 mg, 5 mg, 10 mg, Swedish Orphan Biovitrum International AB was initially approved on the 21/02/2005 and hence its market exclusivity has expired.

The indication as finally proposed for Nityr is in accordance with the reference product's SmPC, except for the statement "in any age range". The indication as approved for Nityr is: "Treatment of adult and paediatric patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine."

To support the application, the applicant has submitted 1 pivotal bioequivalence study (CT-003), 1 pivotal food effect study (CT-002) and one supporting pharmacokinetic study that investigated the bioavailability of Nitisinone Cycle (CT-001).

In the pivotal bioequivalence study (CT-003) Nitisinone Cycle 10 mg tablets are compared to ORFADIN capsules 10 mg (Reference Medicinal Product, RMP). For the lower strengths (2 mg and 5 mg), Cycle had requested a biowaiver in accordance with the "Guideline on the investigation of bioequivalence", which was not granted.

Nityr tablets are administered orally. The recommended initial dose in the paediatric and adult population is 1 mg/kg body weight/day. The dose of nitisinone should be adjusted individually up to a dose of 2 mg/kg body weight/day based on the evaluation of all biochemical parameters. For detailed posology and method of administration, please refer to the Product information.

Main safety concern is related to the mode of action of nitisinone and is well reflected in the agreed RMP: increased tyrosine levels, which are the cause of common eye related adverse reactions, such as conjunctivitis, corneal opacity, keratitis, photophobia, and eye pain. Other common adverse reactions include thrombocytopenia, leucopenia, and granulocytopenia. Exfoliative dermatitis may occur uncommonly.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 10 mg of nitisinone as active substance.

Other ingredients are glycerol dibehenate and lactose monohydrate.

The product is available in high-density polyethylene (HDPE) bottles with a tamper-evident child-resistant closure of polypropylene (PP), as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione corresponding to the molecular formula $C_{14}H_{10}F_3NO_5$. It has a relative molecular mass of 329.23 and the following structure:

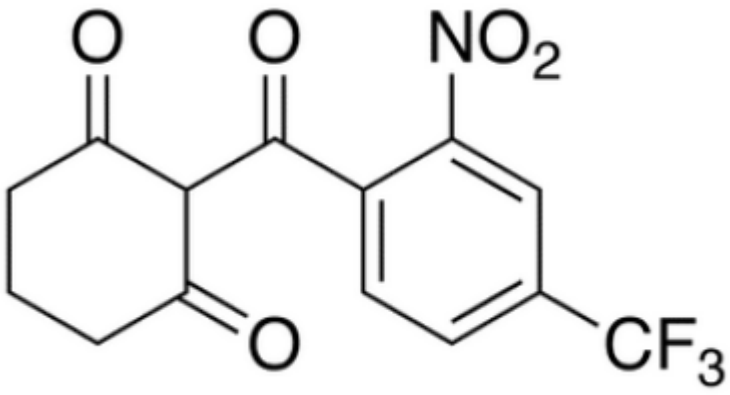

Figure 1: active substance structure

The chemical structure of nitisinone was elucidated by a combination of elemental analysis, mass spectrometry, NMR spectroscopy and UV/IR spectroscopy. An XRPD polymorph investigation study has been performed showing that polymorphism has not been observed for nitisinone. In addition, in a stability study carried out with Nityr tablets, there was no observation in polymorphic change under accelerated stability conditions (40 °C/75% RH) over the 12-month study period.

The active substance is a white to light brown non-hygroscopic powder. It is poorly soluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol. Nitisinone is a weak acid and its solubility increases with pH. It is highly soluble in the pH range 4.5-7.2 in phosphate buffer solutions.

Nitisinone does not exhibit stereoisomerism as it has a non - chiral molecular structure.

Manufacture, characterisation and process controls

Nitisinone is synthesized in three main chemical transformation steps using two commercially available well-defined starting materials with acceptable specifications. The synthesis of the active substance involves reacting the proposed starting materials) to form a non-isolated intermediate which further reacts to form the isolated crude active substance. The chemical steps are followed by crystallisation, isolation and purification steps. While the synthesis is short, the acceptability of the synthesis was thoroughly justified at the request of CHMP including factors such as the control of the starting materials, control of the synthesis steps and intermediates, and the ability of the synthesis to purge potential impurities.

The occurrence and control of impurities in the active substance from the starting materials, impurities in the starting materials and reagents has been evaluated and the information regarding these has been supplemented during the procedure at the request of CHMP. The potential impurities that may be present in the starting materials are discussed and the likelihood of these impurities progressing through the synthesis and further reacting has been considered. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

An evaluation of the mutagenic potential of these potential impurities (from the starting materials, impurities in the starting materials and reagents) has been conducted in accordance with ICH M7. Where an impurity has been observed in the synthesis or where that impurity has been identified as being of mutagenic concern a control is in place in the starting material specification to limit this impurity. The side reactions possible from impurities in the synthesis have been discussed and based on the discussion provided, the controls on the original impurities and the absence of any reported levels of these impurities, found acceptable.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

No important changes have been introduced during the development of the manufacturing process.

The active substance is packaged in a sealed polythene bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended. This bag is then placed inside another sealed polythene bag. The material is then held in a fibreboard cask with a fibreboard lid.

Specification

The active substance specification includes tests for: appearance, identity (IR, UV, HPLC), assay (HPLC), purity (HPLC), impurities (HPLC, GC), sulphated ash (Ph. Eur.), residual solvents (GC), water content (KF) and particle size distribution (laser diffraction).

The analytical methods used have been adequately described appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from one pilot scale and 6 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions heat/humidity, photolysis oxidation, acid and base conditions were also provided on one batch.

The following parameters were tested: appearance, identity, assay, purity, impurities, sulfated ash, residual solvents and water content. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. Assay decreased under photolytic and oxidative stress testing and degradation products increased under oxidative and base stress testing.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Nityr tablets are an immediate-release solid oral dosage form, presented as white to beige, round flat tablet (7 x 2.3 mm), which may display light yellow to brown speckles marked with the tablet strength (10) on one side and 'L' on the other side.

The aim of development was to produce an oral solid dosage form of nitisinone bioequivalent to the originator product Orfadin capsules 10 mg. The desired formulation should additionally possess the following attributes: acceptable and complete dissolution release, the correct amount of active substance in each tablet, stability, purity and acceptable appearance.

Particle size of the active substance is not known to affect the manufacturability or dissolution performance of Nityr tablets. A polymorphism study was carried out to investigate the potential polymorphic change of the active substance in the finished product. Data confirmed that no polymorphic change has been observed in the finished product after 6 months of storage under accelerated conditions.

Nitisinone has low solubility (< 0.04 mg/mL) below pH 5. The solubility increases with pH from 0.4 mg/mL at pH 5 to 41 mg/mL at pH 8. The dissolution of the finished product in phosphate buffer pH 6.8 reaches more than 90% in 30 minutes at release. In accordance with the Ph. Eur. 5.17.1 requirements and batch data, CHMP requested that the release specification for dissolution testing is amended to "Q=80% in 30 minutes" during the procedure. This is consistent with the recommendations in Reflection paper on the dissolution specification for generic oral immediate release products (EMA/332805/2016).

The discriminatory power of the dissolution method has been investigated by introducing changes to both the manufacturing process (e.g. resulting in different tablet hardness) and formulation (e.g. change in levels of lubricant glyceryl dibehenate) and it has been demonstrated in a satisfactory manner. The dissolution method employs Apparatus II (Paddle), 900 mL of pH 6.8 buffer and 50 rpm paddle speed.

During the development, a cyclization degradation pathway of nitisinone was identified, and this intramolecular cyclization reaction was shown to be accelerated by elevated temperature.

The final commercial formulation has shown good stability and does not require refrigeration like the originator.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The formulation used during clinical studies is the same as that intended for marketing and the manufacturing processes are similar, as the manufacturing process involves only blending and compression steps.

A pivotal, three-way crossover bioequivalence study was carried out with the reference product, generic medicinal product and aged generic medicinal product. The statistical analysis showed that both standard generic medicinal product and aged generic medicinal product are bioequivalent to the reference medicinal product. The reference and generic products differ in terms of the dosage form (capsules vs tablets, respectively) and excipients (pregelatinised starch, gelatin capsules and printing ink vs glyceryl dibehenate and lactose, respectively), however the bioequivalence study demonstrated that the products were equivalent.

Dry blending and direct compression were chosen as the finished product manufacturing steps. The manufacturing development was initiated at lab scale and subsequently transferred to a scale-up lab using the proposed commercial manufacturing equipment. Following the successful manufacture of the finished product in the scale-up lab, the manufacturing process was determined, and three batches of the finished product were manufactured at commercial scale for validation.

The primary packaging is high-density polyethylene (HDPE) 75 mL square bottles with a tamper-evident child-resistant closure of polypropylene (PP). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of two main steps: blending and tabletting. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), average mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (KF), assay (HPLC), related substances (HPLC), dissolution (in-house) and microbial purity (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Supportive stability study under intermediate stability conditions was also carried out. In addition, supportive stability data is also provided for development batches stored under long term conditions for 18 months. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Matrixing (one-third reduction design) has been applied to the long term stability study as per ICH Q1D.

Samples were tested for appearance, water content, assay, related substances, dissolution and microbial purity. The analytical procedures used are stability indicating. No significant changes have been observed and all the results were within specifications.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Compared to the dark control samples, there is no significant change in the product quality (appearance, assay, related substance, water content and dissolution) when the tablets are stored in the commercial primary packaging and exposed to the light source. However, slight discoloration has been observed when tablets were exposed to the light source directly. In addition, new unknown impurities were observed in related substance testing, but all of them are below reporting threshold. The side of the tablets that was exposed to the light source turned from white/off-white to light yellow-cream. It is therefore concluded that the product should be stored in primary packaging and avoid light exposure.

The in-use shelf life is set to 2 months based on the conclusion of in-use stability report. The finished product was subjected to a simulated in-use stability study. At different time-points tablets were removed from the bottle to simulate the headspace from the real world use, the bottles were opened daily and samples were analysed immediately after being taken out of the packaging. Based on the results, the statement “During the shelf life, the patient may store the open bottle for a period of 2 months, after which the medicinal product must be discarded.” is included in the Product Information.

Based on available stability data, the proposed shelf-life of 36 months and no special temperature storage conditions, but stored in the original bottle to protect from light as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of

ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure significant additional information regarding the selection of starting materials and the active substance impurities was provided at the request of the CHMP. Dissolution specifications were also tightened at CHMP request. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of nitisinone are well known. As nitisinone is a widely used, well-known active substance, the applicant has not conducted additional nonclinical pharmacodynamic, pharmacokinetics, toxicology, reproductive toxicology, genotoxicity or carcinogenicity studies. Overview based on literature review is, thus, appropriate.

Nitisinone has been used to treat HT-1 since 1991, and approved for HT-1 treatment by EMA as ORFADIN capsules in the EU in 2005 (EMEA/H/C/000555), and as ORFADIN suspension in 2015. In the pivotal clinical study performed by Cycle, it has been demonstrated that Nitisinone Cycle is bioequivalent to ORFADIN capsules. Therefore, in this submission, the nonclinical development will rely on the nonclinical data that supported the approval of ORFADIN capsules (EMEA/H/C/000555) by EMA. The only additional information provided by the Company is a genotoxicity in silico analysis.

The rationale for the conduct of the in silico analysis for nitisinone and its metabolites comes from the equivocal previous results which demonstrated that purified nitisinone was mutagenic in mammalian cells (mouse lymphoma forward mutation test) in vitro, while no test for chromosome damage in vitro was performed. Purified nitisinone also produced a weakly positive response in the mouse micronucleus test in vivo. A mouse liver unscheduled DNA synthesis (UDS) assay in vivo was subsequently performed in light of the positive genotoxicity results obtained and presence of structural alerts (electrophilic centres and an

aromatic nitro group) for nitisinone. This study showed no evidence of DNA damage in vivo. Based on the in silico analysis and the combined evidence from the empirical evidence coupled with expert judgement neither nitisinone nor oxotetrahydroxanthone should be considered bacterial mutagens. As such these structures should be classified as class 5 under ICH M7. It is not expected that oxotetrahydroxanthone would induce additional toxicity to that shown by nitisinone.

The present nonclinical literature review does not bring any additional data that from the regulatory point of view would change the safety profile of nitisinone in its present clinical use.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

Environmental risk assessment has been carried out according to the present guidelines and does not cause any additional risks, because in the Tier I analysis the calculated PECsurfacewater value is below the action limit, 0.01 µg/L.

2.3.3. Conclusion on the non-clinical aspects

A non-clinical overview has been provided and was based on up-to-date and adequate scientific literature, a genotoxicity in silico analysis and environmental risk assessment. The CHMP considered this application acceptable from non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for tablets containing nitisinone. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment (CT-003). Furthermore 2 supportive studies were submitted, i.e. one food effect study (CT-002) and one supporting pharmacokinetic study that investigated bioavailability of Nitisinone Cycle (CT-001).

In the pivotal bioequivalence study (CT-003) Nitisinone Cycle 10 mg tablets are compared to ORFADIN capsules 10 mg (Reference Medicinal Product, RMP).

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Exemption

For the lower strengths (2 mg and 5 mg) initially applied for, the applicant had requested a biowaiver in accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

2.4.2. Pharmacokinetics

To support the application, the applicant has submitted 1 pivotal bioequivalence study (CT-003), 1 pivotal food effect study (CT-002) and one supporting pharmacokinetic study that investigated the bioavailability of Nityr (CT-001).

In the pivotal bioequivalence study (CT-003) Nityr 10 mg tablets are compared to ORFADIN capsules 10 mg (Reference Medicinal Product, RMP). In general, the 3 submitted studies were similar in design, study population, dosing, sampling schedules, analytical and statistical methods, PK variables measured and safety data generated.

- ***Tabular overview of clinical studies***

Pharmacokinetic and bioequivalence study summary for Nitisinone Cycle

Study type	Study number	Study design	Subject number	IMP*	Results
Pivotal bioequivalence study	CT-003	3-way crossover, 3-period, 3-treatment bioequivalence study	23	ORFADIN capsules 10 mg Nitisinone Cycle tablets 10 mg Aged Nitisinone Cycle tablets 10 mg	Bioequivalence was established between ORFADIN capsules and both Nitisinone tablets formulations.
Pivotal food effect study	CT-002	2-way crossover, 2-period food effect study	19	Nitisinone tablets 10 mg	No statistical difference between the pharmacokinetic of Nitisinone tablets administered under fasted and fed conditions.
Pharmacokinetic study	CT-001	3-way crossover, 3-period, 3-treatment bioequivalence study	23	ORFADIN capsules 10 mg Nitisinone Cycle tablets 10 mg High Compritol Nitisinone Cycle tablets 10 mg	Bioequivalence was established between ORFADIN capsules and both Nitisinone tablets formulations.

CT-003: Study PXL227430

A single centre, single dose, open-label, laboratory blind, randomised, three period crossover study to determine the bioequivalence of two oral formulations containing nitisinone 10mg to the reference formulation Orfadin® 10mg in at least 18 healthy male and female subjects under fasting conditions.

Methods

Study design

This was a single-dose, open-label, laboratory-blind, randomized, three-period crossover study with orally administered nitisinone 10 mg (2 test products and a reference product) conducted under fasting conditions in at least 18 healthy male and female subjects at a single study centre.

Primary objective

To determine whether the test products (nitisinone 10 mg tablets and nitisinone 10 mg tablets [6 months @ 40°C/75% RH]), and the reference product, Orfadin® 10 mg hard capsules are bioequivalent.

Design

The study comprised:

Screening period of maximum 21 days;

Three treatment periods (each of which included a profile period of 120 hours) separated by a wash-out period of 23 to 24 calendar days between consecutive administrations of the investigational medicinal product (IMP), and

A post-study visit within 72 hours of completion of the last treatment period of the study. The slit lamp examination at post-study was scheduled up to 7 days of completion of the last period of the study.

Subjects received all three products according to a treatment sequence as randomized. After an overnight fast of at least 10 hours, subjects received either the reference product (Treatment A) Test Product 1 (Treatment B) or Test Product 2 (Treatment C) according to the randomization schedule with 240 mL water. The IMP was swallowed whole with water. Aged Nityr tablets (stored at 40°C/75% RH for more than 6 months) were administered to investigate the effect of prolonged dissolution time of Nityr on bioavailability.

Reference product (Treatment A, Orfadin 10mg)

Test Product 1 (Treatment B, Nitisinone Tablets 10mg, manufactured by Rivopharm SA)

Test Product 2 (Treatment C, Nitisinone Tablets 10mg, 6 months @ 40°C/75% RH, manufactured by Rivopharm SA)

Study Duration:

Three treatment periods (each including a profile period of 120 hours), each starting with a 24-hour clinic day and a wash-out period of 23 to 24 calendar days between clinic days. The duration of this study was approximately 66 days (9 weeks) per subject (excluding the screening period).

Dosing:

The dosage in this study included a single oral dose of nitisinone 10 mg, on each of three separate occasions, under fasting conditions.

The dose administered in this study was lower than the usual dose of nitisinone which is 1 to 2 mg/kg divided into two daily doses.

Sampling Schedule:

Pharmacokinetic blood samples were collected at the following time points: at pre-dose (0 hours) and at 15 minutes, 30 minutes, 1 hour, 2 hours, 2 hours 30 minutes, 3 hours, 3 hours 30 minutes, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours and 120 hours post-dose (total: 21 samples per treatment period). The actual blood sampling times were recorded on source data and attached to the CRFs.

Subjects were allowed to leave the study centre 24 hours after administration of IMP, providing they returned for the subsequent blood sample collection as instructed by the study staff.

Venous blood samples, 6 mL each, for the determination of nitisinone in plasma concentrations were collected into labeled ethylenediaminetetraacetic acid (EDTA) plastic tubes.

Table 4:

Total Blood Volume Collected during the Study

Assay	Volume per sample (*mL*)	Total number of samples	Total blood volume (*mL*)
Nitisinone[†]	6	21 x 3	126 x 3
Hematology	4	2	8
Clinical chemistry[*]	5	2	10
Total blood volume (entire study)[**]			396

[†]Total number of samples and total blood volume are given per treatment period

[*]Serum pregnancy tests (females only) and serology tests at screening were performed on the sample collected for clinical chemistry

[**]Excluding repeat laboratory investigations

Test and reference products

Subjects received all three products according to a treatment sequence as randomized. After an overnight fast of at least 10 hours, subjects received either the reference product (Treatment A, Orfadin 10mg, manufactured by Apotek Produktion & Laboratorier AB, Batch No 3041069, Exp 31/01/17) Test Product 1 (Treatment B, Nitisinone Tablets 10mg, manufactured by Rivopharm SA, Switzerland, Batch No 151159, Exp 10/06/16) or Test Product 2 (Treatment C, Nitisinone Tablets 10mg, 6 months @ 40°C/75% RH, manufactured by Rivopharm SA, Switzerland, Batch No TF0015/16, Exp 19/03/16) according to the randomization schedule with 240 mL water. The IMP was swallowed whole with water.

Population(s) studied

Healthy males and females, 18 to 55 years inclusive, BMI between 18.5 and 30 kg/m2, non-smokers, who were judged to be healthy based on a medical history, electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements and willing to use an acceptable, effective method of contraception.

One female subject was withdrawn from the study during Treatment period 1 because she vomited before 2times median t_{max} (pre-defined criteria in protocol for removal of subject from study). Twenty-three subjects (21 males and 2 females) completed both treatment phases.

Protocol deviations are not likely to have influenced the outcome of the study.

Analytical methods

The analytical methods are acceptable; the method underwent pre-study validation. The validation was performed according to the requirements of the EMA “Guideline on bioanalytical method validation” (EMEA/CHMP/EWP/192217/2009). Intra-run calibration standard accuracy was performed during sample analyses. Sample handling is acceptable. Certificate of Analysis for reference standards were provided. A statement on GCP compliance in addition to a Quality Assurance Statement regarding adherence to the study protocol and SOPs was included.

The bioanalytical method demonstrates acceptable performance and is suitable for the determination of Nitisinone in EDTA human plasma over the calibration range.

Pharmacokinetic Variables

Calculation of the PK parameters was made with Phoenix® WinNonlin® 6.3 (Certara, L.P., 1699 South Hanley Road, St Louis, Missouri 63144, USA). All AUCs were calculated using the linear trapezoidal rule.

The PK parameters were calculated for each subject and treatment using non-compartmental analysis and using the actual sampling time intervals (relative to IMP administration).

Primary Pharmacokinetic Parameters

Maximum observed plasma concentration (C_{max})

AUC from time zero to 120 hours post-dose ($AUC_{(0-120)}$)

Secondary Pharmacokinetic Parameters

AUC from time zero to 72 hours post dose ($AUC_{(0-72)}$)

AUC with extrapolation to infinity ($AUC_{(0-\infty)}$)

Time to maximum observed plasma concentration (t_{max})

Terminal elimination rate constant (λ_z)

Apparent terminal elimination half-life ($t_{½}$)

The test products were compared to the reference product with respect to the primary PK parameters for nitisinone, using an ANOVA with sequence, subject (sequence), treatment and period as fixed effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "test/reference" geometric mean ratios of these primary PK parameters were calculated.

Criteria for Evaluation:

The 90% CIs of the relative mean plasma $AUCt_{(0-120)}$ and C_{max} of the test to reference products should be between 80.00 and 125.00%.

Statistical methods

The data listings, descriptive statistics, statistical analysis and graphs of this study were generated using SAS/STAT® and SAS/GRAPH® software.

The test products were compared to the reference product by means of statistical analysis with respect to the primary PK parameters using an analysis of variance with sequence, subject (sequence), product and period

effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "test/reference" geometric mean ratios of these parameters were tabulated.

Bioequivalence of the test and reference products were assessed on the basis of the 90% confidence intervals for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products using an analysis of variance considering the bioequivalence range of 80.00% to 125.00% for Cmax and AUC(0-120).

Randomisation

Twenty-four (24) subjects were enrolled and randomized to a 6 sequence Williams design for 3 periods and 3 treatments (ABC, BCA, CAB, ACB, BAC and CBA) in order to complete the study with at least 18 subjects.

Determination of Sample size

Based on a bioequivalence range of 80.00% to 125.00% for Cmax and AUC(0-120), assuming a "test/reference" mean ratio between 0.95 and 1.05, 18 subjects were needed to achieve a power of 80% at an alpha level of 0.05 to show bioequivalence for this 3-period study.

Results

Table 5: Pharmacokinetic parameters for Nitisinone (non-transformed and ln-transformed values)

PK Parameter (unit)	LS Mean			Mean Ratio (%)	90% Confidence Interval of Ratio
	Orfadin® (Reference product)	Nitisinone (Test product 1)	Nitisinone (Test product 2)		
Test 1 vs Reference					
$AUC_{(0-120)}$ (h•ng/mL)	78149.092	78040.865	NA	99.86	96.34 ; 103.51
$AUC_{(0-72)}$ (h•ng/mL)	58646.164	57948.259	NA	98.81	95.63 ; 102.09
C_{max} (ng/mL)	1333.510	1278.828	NA	95.90	91.66 ; 100.34
t_{max} (h)*	2.50	3.50	NA		p-value: 0.2300
Test 2 vs Reference					
$AUC_{(0-120)}$ (h•ng/mL)	78090.254	NA	77187.852	98.84	94.75 ; 103.11
$AUC_{(0-72)}$ (h•ng/mL)	58600.801	NA	57455.264	98.05	93.98 ; 102.28
C_{max} (ng/mL)	1332.941	NA	1273.675	95.55	91.14 ; 100.19
t_{max} (h)*	2.50	NA	3.90		p-value: 0.0258

PK – pharmacokinetic; LS = least square mean; CV = coefficient of variation; NA = not applicable
*Median

CT-002: Study PXL-225421

A single centre, single-dose, open-label, laboratory-blind, randomized, two-period crossover study to determine the comparative bioavailability of an oral formulation containing of nitisinone 10 mg in at least 16 healthy male and female subjects under fasted and fed conditions.

Methods

Study design

This was a single-dose, open-label, laboratory-blind, randomized, two-period crossover study with orally administered nitisinone 10 mg conducted under fasting and fed conditions in 19 healthy male and female subjects at a single study centre.

Primary objective

To assess the comparative bioavailability of Nityr tablets in healthy subjects under fasted and fed conditions (food-effect).

Design

The study comprised:

Screening period of maximum 21 days;

Two treatment periods (each of which included a profile period of 120 hours) separated by a wash-out period of 23 calendar days between consecutive administrations of the investigational medicinal product (IMP).

A post-study visit within 72 hours of completion of the last treatment period of the study. The slit lamp examination at post-study was scheduled up to 7 days of completion of the last period of the study.

Subjects were assigned randomly to a condition (fasting, then fed or fed, then fasting) sequence, before the first administration of IMPs.

Before dosing, subjects were randomized into two groups (50/50 randomization). The first group received the IMP after a high-calorie, high fat breakfast in Treatment period 1, while the second group received the IMP after a high-calorie, high fat breakfast in Treatment period 2.

Study Duration:

The duration of this study was approximately 31 days (4½ weeks) per subject (excluding the screening period). The actual overall study duration and study recruitment time varied.

Each treatment period included a profile period of 120 hours, which commenced with morning dosing of IMP on a 24-hour clinic stay at the study centre.

Subjects were admitted to the study centre on Day -1 to ensure an overnight fast of at least 10 hours before dosing.

Dosing:

In compliance with bioavailability/bioequivalence guidelines, the dosage in this study included a single oral dose of nitisinone 10 mg, on each of 2 separate occasions, under fed and fasting conditions, respectively.

The dose administered in this study was lower than the usual dose of nitisinone which is 1 to 2 mg/kg divided into two daily doses.

Sampling Schedule:

Pharmacokinetic blood samples were collected and stored according the same schedule and methods as seen in CT-003 in both arms.

General Dietary restrictions:

The IMP was administered in the standing position. Posture control procedures were documented.

The ingestion of food and beverages containing citrus fruits and/or apple or pineapple was not allowed for 72 hours before the administration of IMP and until the last PK blood sample was collected per treatment period.

The ingestion of food and beverages containing alcohol and/or methylxanthines e.g., caffeine (coffee, tea and cola) was not allowed for 24 hours before the administration of IMP and until the last PK blood sample was collected per treatment period.

Food and beverage intake during the clinic stay was standardized per treatment period. Meals taken after dosing were standardized in regard to composition and time of administration.

Water was allowed as desired except for 1 hour before and 1 hour after IMP administration and no food was allowed for at least 4 hours post-dose.

For subjects randomized into the fed treatment period, a high-fat, high-calorie breakfast was served 30 minutes before administration of the IMP. The whole meal was consumed within 30 minutes.

Strenuous physical activity was not allowed for 24 hours before the start of each clinic day and until the last PK blood sample was collected per treatment period.

- **Table 6: Prescribed meal**

The following table summarizes the recipe constituents for a high-fat, high-calorie breakfast:

Food	Amount (g)	Energy (cal)	Carbohydrate (g)♦	Protein (g)	Fat (g)
Tomato	50	10.8	2.0	0.4	0.1
Butter	16	115.8	0.0	0.1	13.1
Milk – whole, fresh	200	124.7	9.6	6.4	6.8
Potato croquette	70	153.5	12.1	1.8	11.1
Omelet – plain, using whole milk	120	180.8	2.3	12.1	13.9
Bacon	40	223.7	0.2	12.2	19.7
Bread rolls – whole wheat	70	180.3	35.6	5.8	1.5
TOTAL		989.8	61.8	38.8	66.1
Energy (%)			24.8	15.6	60.0
Energy (cal)			250.1	157.0	566.5
Energy (cal) per FDA requirements		800-1000	250	150	500-600

♦ Carbohydrate value includes fiber.

Test and reference products

Subjects received the test product once under fasting conditions and once under fed conditions.

Subjects in the fasting treatment period received the test product (according to the randomization schedule) with 240 mL water after an overnight fast of at least 10 hours. Subjects in the fed treatment period fasted for at least 10 hours overnight, and received the test product 30 minutes after consuming a high-calorie, high-fat breakfast. The tablet of nitisinone was swallowed whole with water.

Test Product

Generic name: Nitisinone

Dosage form: Tablets

Dose: 10 mg (1 tablet)

Route of administration: Oral

Manufacturer: Rivopharm SA, Switzerland

Batch number: 151159

Retest date: 21 November 2015. 01 January 2016 (updated certificate of analysis)

Assayed product content: 102%. 100% (updated certificate of analysis)

Population(s) studied

Healthy males and females, 18 to 55 years inclusive, BMI between 18.5 and 30 kg/m2, non-smokers, who were judged to be healthy based on a medical history, electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements, willing to consume the prescribed meal and willing to use an acceptable, effective method of contraception.

Twenty subjects (17 males and 3 females) were screened and entered into the study. One female subject withdrew from the study after Treatment period 1 for personal reasons. Nineteen subjects (17 males and 2 females) completed both treatment phases.

Seventeen male and two female subjects completed the study. Two subjects were Caucasian and 17 subjects were Black.

Protocol deviations are not likely to have influenced the outcome of the study.

Analytical methods

As per CT-003

Pharmacokinetic variables

- *Primary Pharmacokinetic Parameters*
  - Maximum observed plasma concentration (C_{max})
  - Area under the plasma concentration versus time curve, from time zero to 120 hours post-dose ($AUC_{(0-120)}$)
- *Secondary Pharmacokinetic Parameters*
  - AUC from time zero to 72 hours post dose ($AUC_{(0-72)}$)
  - AUC with extrapolation to infinity ($AUC_{(0-\infty)}$)
  - Time to reach maximum observed plasma concentration (T_{max})
  - Terminal elimination rate constant (λ_z)
  - Apparent terminal elimination half-life ($t_{½}$)

The test product was compared under fasting and fed conditions by means of statistical analysis with respect to the primary PK parameters using an analysis of variance (ANOVA) with sequence, subject (sequence), fed/fasting and period effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "fed/fasting" geometric mean ratios of these parameters are tabulated.

- *Criteria for Evaluation:*

Bioavailability of the test product under fasting and fed conditions was assessed on the basis of the 90% confidence intervals for estimates of the geometric mean ratios between the primary PK parameters of the test product under fasting and fed conditions using an analysis of variance considering the conventional range of 80.00% to 125.00% for C_{max} and $AUC_{(0-120)}$

A non-parametric Wilcoxon signed rank test was performed on the variable T_{max} for the test product under fasting and fed conditions differences and the results were tabulated.

Statistical methods

All subjects for whom primary PK parameters C_{max} and $AUC_{(0-120)}$ were planned to be calculated for both treatment periods and who had no major protocol deviations thought to impact on the analysis of the PK data were included in the statistical PK analysis for the study.

The individual plasma nitisinone concentration versus actual time profiles for each subject and treatment (fast or fed), as well as the mean plasma (arithmetic and geometric) plasma nitisinone concentration versus scheduled time profiles for each treatment (fast or fed), are presented graphically on a linear-linear and log-linear scale. Individual plasma concentrations are presented using actual, rather than planned, sampling times. Combined individual concentration versus time graphs per treatment (fast or fed) are presented on a linear-linear scale, together with the geometric mean values. The individual log-linear graphs reflecting the WinNonlin modeling results, are presented using SAS.

The data listings, descriptive statistics, statistical analysis and graphs of this study were generated using SAS/STAT® and SAS/GRAPH® software.

Randomisation

The randomization schedule was generated utilizing the PROC PLAN procedure of SAS software.

Subjects will be randomized to one of two treatment sequences (fasting, then fed or fed, then fasting) and were assigned randomization numbers 01 – xx, sequentially.

Determination of Sample size

Upon request of the sponsor, 20 eligible subjects were entered into the study, to complete the study with at least 16 evaluable subjects.

This corresponded to the following:

Based on the conventional range of 80.00% to 125.00% for C_{max} and $AUC_{(0-120)}$ and a "fed/fasting" mean ratio between 0.95 and 1.05, 16 subjects are needed to achieve a power of 80% at an alpha level of 0.05 to compare bioavailability

Results

The test product was compared under fasting and fed conditions by means of a statistical analysis with respect to the primary PK parameters using an ANOVA with sequence, subject (sequence), treatment and

period effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "fed/fasting" geometric mean ratios of these parameters are tabulated.

Table 7: Summary of Statistical Analyses of Plasma Nitisinone Pharmacokinetic Parameters (Number of Observations = 38)

Parameter (unit)	LS Mean		Mean Ratio (Fed/Fast) (%)	90% Confidence Interval of Ratio
	Nitisinone (Fed)	Nitisinone (Fast)		
$AUC_{(0-120)}$ (h•ng/mL)	67508.639	70841.080	95.30	92.71 ; 97.95
$AUC_{(0-72)}$ (h•ng/mL)	49966.954	52560.003	95.07	92.70 ; 97.50
C_{max} (ng/mL)	1056.884	1159.960	91.11	86.56 ; 95.91
λ_z (1/h)	0.012	0.011	0.07	-0.05 ; 0.19
T_{max} (h)	6.186	3.900	228.61	104.26 ; 352.96
T_{max} (h)*	6.00	3.00		p-value: 0.0048

LS = least square mean; CV = coefficient of variation
*Median

Bioavailability was based on the PK parameters of AUC(0-72) and AUC(0-120). The mean ratio (Fed/Fast) of the AUC(0-120) was 95.30% with a 90% confidence interval (CI) 92.71% and 97.95%. Under the fed state, the AUC(0-120) coefficient of variation was reduced from 26.4% (fasted) to 17.1%. The mean ratio (Fed/Fast) of the AUC(0-72) was 95.07% with 90% CI 92.70% and 97.50%. Under the fed state, the AUC(0-72) coefficient of variation was reduced from 25.0% (fasted) to 16.8%.

Following single-dose administration of the IMP, maximum plasma concentrations of nitisinone were reached at a median of 6 hours post-dose under fed conditions and 3 hours post-dose under fasting conditions (p-value = 0.0048).

The point estimates of the "Fed/Fast" mean ratios of the PK parameters Cmax, AUC(0-72) and AUC(0-120) for nitisinone are 91.11%, 95.07% and 95.30%, respectively.

The 90% CI for the "Fed/Fast" mean ratios of the PK parameters Cmax, AUC(0-72), and AUC(0-120) for nitisinone are 86.56% to 95.91%. 92.70% to 97.50%, and 92.71% to 97.95%, respectively.

CT-001: Study PXL-225418

A single centre, single-dose, open-label, laboratory-blind, randomized, three-period crossover study to determine the comparative bioavailability of two oral formulations containing of nitisinone 10 mg in at least 16 healthy male and female subjects under fasted conditions.

Methods

Study design

This was a single-dose, open-label, laboratory-blind, randomized, two-period crossover study with orally administered nitisinone 10 mg (two test formulations and a reference product) conducted under fasting and fed conditions in 18 healthy male and female subjects at a single study centre.

Background

The clinical study was performed in Bloemfontein (South Africa). The sponsor was Cycle Pharmaceuticals Ltd. The study report states that the study was conducted in accordance with ICH GCP and the Declaration of Helsinki. The study period was from 15/10/15 to 22/01/16.

Primary objective

To determine whether the test products (nitisinone 10 mg tablets and nitisinone 10 mg high compritol tablets), and the reference product, Orfadin® 10 mg hard capsules are bioequivalent.

Design

The study comprised:

- Screening period of maximum 21 days;
- Three treatment periods (each of which included a profile period of 120 hours) separated by a wash-out period of 23 calendar days between consecutive administrations of the investigational medicinal product (IMP)
- A post-study visit within 72 hours of completion of the last treatment period of the study. The slit lamp examination at post-study was scheduled up to 7 days of completion of the last period of the study.

Subjects were assigned randomly to treatment sequence according to the randomization schedule, before the first administration of IMP.

Study Duration:

The duration of this study was approximately 66 days (~9 weeks) per subject (excluding the screening period). The actual overall study duration and study recruitment time varied.

Each treatment period included a profile period of 120 hours, which commenced with morning dosing of IMP on a 24-hour clinic stay at the study centre.

Subjects were admitted to the study centre on Day -1 to ensure an overnight fast of at least 10 hours before dosing.

Dosing:

In compliance with bioavailability/bioequivalence guidelines, the dosage in this study included a single oral dose of nitisinone 10 mg, on each of 3 separate occasions, under fasting conditions.

A mouth check was performed after each dosing by the principal investigator or designee to ensure that the subjects had swallowed the IMP.

Water was allowed as desired except for 1 hour before and 1 hour after IMP administration and no food was allowed for at least 4 hours post-dose.

The ingestion of food and beverages containing citrus fruits and/or apple or pineapple was not allowed for 72 hours before the administration of IMP and until the last PK blood sample was collected per treatment period.

Sampling Schedule:

Pharmacokinetic blood samples were collected and stored according the same schedule and methods as the previous studies. CT –002 and CT 003.

General Dietary restrictions and physical activity:

This was the same as study 002.

Test and reference products

Reference Product (Treatment A)

Generic name	:	Nitisinone
Trade name	:	Orfadin® 10 mg
Dosage form	:	Hard capsules
Dose	:	10 mg (1 capsule)
Route of administration	:	Oral
Manufacturer	:	Apotek Produktion & Laboratorier AB, Sweden
Country of origin	:	Sweden
Batch number	:	3036405
Expiry date	:	31 May 2016
Assay content	:	99% (see analytical result summary presented in Appendix 16.1.6)

Test Product 1* (Treatment B)

Generic name	:	Nitisinone
Dosage form	:	Tablets
Dose	:	10 mg (1 tablet)
Route of administration	:	Oral
Manufacturer	:	Rivopharm SA, Switzerland
Batch number	:	151159
Retest date	:	21 November 2015 01 January 2016 (updated certificate of analysis)
Assay content	:	102% 100% (updated certificate of analysis)

Test Product 2* (Treatment C)

Generic name	:	Nitisinone
Dosage form	:	Tablets (high compritol)
Dose	:	10 mg (1 tablet)
Route of administration	:	Oral
Manufacturer	:	Rivopharm SA, Switzerland
Batch number	:	151160
Retest date	:	20 November 2015 01 January 2016 (updated certificate of analysis)
Assay content	:	101% 98% (updated certificate of analysis)

Population(s) studied

Healthy males and females, 18 to 55 years inclusive, BMI between 18.5 and 30 kg/m2,

Body mass not less than 50 kg, non-smokers, who were judged to be healthy based on a medical history, electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements, willing to consume the prescribed meal and willing to use an acceptable, effective method of contraception.

Twenty-four subjects (19 males and 5 females) were screened and entered into the study. One male subject was withdrawn from the study on 26 October 2015 (Day 1 of Treatment period 1) because he vomited. Twenty-three subjects (18 males and 5 females) completed the study.

Deviations from the scheduled sampling times for collection of the PK blood samples were presented in the dossier. These deviations are not likely to have influenced the outcome of the study.

Analytical methods

As per CT-003

Pharmacokinetic variables

Calculation of the PK parameters was made with Phoenix® WinNonlin® 6.2 (or higher) (Certara, L.P., 1699 South Hanley Road, St Louis, Missouri 63144, USA).

The PK parameters were calculated for each subject and treatment using non-compartmental analysis and using the actual sampling time intervals (relative to IMP administration).

Primary Pharmacokinetic Parameters

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration versus time curve, from time zero to 120 hours post-dose ($AUC_{(0-120)}$)

Analysis of Bioequivalence

The statistical analysis was conducted separately for the following:

- Treatment B (Test Product 1) versus Treatment A (Reference Product)
- Treatment C (Test Product 2) versus Treatment A (Reference Product)

Only the data for the comparison under investigation were included in the statistical analysis i.e., when comparing Treatment A and Treatment C, the data for Treatment B were removed from the dataset.

Subjects had to have the primary PK parameters Cmax and AUC(0-120) available for both treatments in order to be included in a specific analysis; a subject was therefore included in 1 or 2 comparisons for a given parameter.

The test products were compared to the reference product by means of statistical analysis with respect to the primary PK parameters using an analysis of variance (ANOVA) with sequence, subject (sequence), treatment and period effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "test/reference" geometric mean ratios of these parameters were tabulated.

Criteria for Evaluation:

Bioavailability of the test product under fasting and fed conditions was assessed on the basis of the 90% confidence intervals for estimates of the geometric mean ratios between the primary PK parameters of the test product under fasting and fed conditions using an analysis of variance considering the conventional range of 80.00% to 125.00% for C_{max} and $AUC_{(0-120)}$

For submission to the FDA, a non-parametric Wilcoxon signed rank test was performed on the variable T_{max} for the test product under fasting and fed conditions differences and the results were tabulated.

Statistical methods

All subjects for whom the primary PK parameters Cmax and AUC(0-120) could be calculated for at least two treatment periods (where one of the treatment periods needed to be the period in which the subject received the Reference product [Treatment A]), and who had no major protocol deviations thought to impact on the analysis of the PK data were included in the statistical PK analysis for the study.

Data from subjects who experienced vomiting during the course of the study were deleted from the statistical analysis if vomiting occurred at or before 2 times median Tmax.

The individual plasma nitisinone concentration versus actual time profiles for each subject and treatment, as well as the mean plasma (arithmetic and geometric) plasma nitisinone concentration versus scheduled time profiles for each treatment (fast or fed), are presented graphically on a linear-linear and log-linear scale. Individual plasma concentrations are presented using actual, rather than planned, sampling times. Combined individual concentration versus time graphs per treatment (fast or fed) are presented on a linear-linear scale, together with the geometric mean values. The individual log-linear graphs reflecting the WinNonlin modeling results, are presented using SAS.

The data listings, descriptive statistics, statistical analysis and graphs of this study were generated using SAS/STAT® and SAS/GRAPH® software

Randomisation

A randomization schedule was provided by PAREXEL Biostatistics. The randomization schedule was generated utilizing the PROC PLAN procedure of SAS® software.

Subjects were randomized to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, CBA) and were assigned randomization numbers 01 to 24.

The subject who was withdrawn from the study was not replaced.

Determination of Sample size

Upon request of the Sponsor, 24 subjects were enrolled and randomized to a 6 sequence Williams design for 3 periods and 3 treatments (ABC, BCA, CAB, ACB, BAC and CBA) in order to complete the study with at least 18 subjects.

This corresponds to the following: Based on a bioequivalence range of 80.00% to 125.00% for Cmax and AUC(0-120) a and a "test/reference" mean ratio between 0.95 and 1.05, 18 subjects were needed to achieve a power of 80% at an alpha level of 0.05 to show bioequivalence [2] for this 3-period study.

Below the Limit of Quantification (BLQ) concentrations will be handled as follows:

This was the same as study CT-002.

Results

The test products was compared under fasting conditions by means of a statistical analysis with respect to the primary PK parameters using an ANOVA with sequence, subject (sequence), treatment and period effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "fed/fasting" geometric mean ratios of these parameters are tabulated.

Table 8: Summary of Statistical Analyses of Plasma Nitisinone Pharmacokinetic Parameters (Number of Observations = 38)

Parameter (unit)	LS Mean			Mean Ratio (%)	90% Confidence Interval of Ratio
	Orfadin® 10 mg tablets (Reference product)	Nitisinone 10 mg tablets (Test Product 1)	Nitisinone 10 mg high compritol tablets (Test Product 2)		
Test 1 vs Reference					
$AUC_{(0-120)}$ (h•ng/mL)	65705.989	66251.703	N/A	100.83	96.58 ; 105.27
$AUC_{(0-72)}$ (h•ng/mL)	49196.050	49408.190	N/A	100.43	96.84 ; 104.15
C_{max} (ng/mL)	1161.934	1136.332	N/A	97.80	93.77 ; 102.00
T_{max} (h)*	2.5	3	N/A		p-value: 0.2034
Test 2 vs Reference					
$AUC_{(0-120)}$ (h•ng/mL)	65798.960	N/A	61998.688	94.22	84.85 ; 104.63
$AUC_{(0-72)}$ (h•ng/mL)	49269.592	N/A	46472.409	94.32	84.58 ; 105.19
C_{max} (ng/mL)	1163.756	N/A	1081.736	92.95	84.03 ; 102.82
T_{max} (h)*	2.5	N/A	3		p-value: 0.1098

Following single-dose administration of the test and reference products, maximum plasma concentrations of nitisinone were reached at a median of 2.5 hours for the reference product and 3 hours post-dose for the test products (p-value for Test 1 vs Reference = 0.2034; p-value for Test 2 vs Reference = 0.1098).

Test 1 vs Reference

The point estimates of the "test/reference" mean ratios of the PK parameters Cmax, AUC(0-72) and AUC(0-120) for nitisinone are 97.80%, 100.43% and, 100.83% respectively.

The 90% confidence intervals for the "test/reference" mean ratios of the parameters Cmax, AUC(0-72) and AUC(0-120) for nitisinone are 93.77% to 102.00%, 96.84% to 104.15% and 96.58% to 105.27% respectively.

Test 2 vs Reference

The point estimates of the "test/reference" mean ratios of the parameters Cmax, AUC(0-72) and AUC(0-120) for nitisinone are 92.95%, 94.32% and 94.22%, respectively.

The 90% confidence intervals for the "test/reference" mean ratios of the parameters Cmax., AUC(0-72) and AUC(0-120) for nitisinone are 84.03% to 102.82%, 84.58% to 105.19% and 84.85% to 104.63%, respectively.

Biowaiver

A biowaiver was sought for the lower strengths (2 mg and 5 mg). Comparative dissolution studies were carried out in four media to demonstrate equivalent drug release to the 10 mg tablet used in the clinical bioequivalence studies. The qualitative and quantitative composition of the test and reference products was compared in the context of the general requirements for a biowaiver of an additional strength from the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). The quantitative composition for the test product (lower strengths) presented a deviation from the requirements in that the amount of the active substance was more than 5 % of the tablet core weight. The applicant was requested to justify this deviation and opinion was sought from the Pharmacokinetics Working Party on the adequacy of

the justification. The justification provided by the applicant was not accepted. The Applicant subsequently withdrew their application for marketing authorisation for the lower strength tablets of 5 mg and 2mg.

Safety data

Study CT-003

No deaths or SAEs were reported during this study and none of the AEs were of severe intensity.

Four subjects had a total of 5 AEs during the study. Two of the events were considered by the investigator to be possibly related to the IMP. All of the events were considered by the investigator to be of mild intensity.

Table 9: Summary of Adverse Events

Subject Number	Preferred Term	Treatment	Relationship	Intensity
08	Influenza	Test 2	Not related	Mild
09*	Vomiting	Reference	Unlikely	Mild
18	Headache	Test 1	Possible	Mild
	Nasopharyngitis	Test 1	Not related	Mild
24	Fatigue	Test 1	Possible	Mild

*Subject withdrawn

No AEs related to laboratory variables were reported, all results outside the normal reference range were assessed as not clinically significant by the investigator or repeated.

Pulse rate and blood pressure remained essentially unchanged throughout the study. Body temperature before dosing on clinic days ranged between 35.5°C and 36.6°C, and no subjects were withdrawn due to pathologically raised body temperature. Results from the 12-lead ECGs performed on all subjects were normal.

No clinically relevant abnormalities were observed in any of the subjects for the physical examinations performed at screening. No abnormal results were reported or the slit lamp eye examinations performed during screening and at post-study.

Study CT-002

The safety population in CT-002 includes 20 subjects who were enrolled and administered at least one dose of an IMP.

No subjects were withdrawn from the study by the investigator. One subject received only 1 dose of the IMP as she withdrew from the study after completion of Treatment period 1 because of personal reasons.

All 20 subjects who were enrolled and administered at least one dose of IMP were included in the safety analysis.

No SAEs or deaths were reported during this study and none of the AEs were of severe intensity. No AEs related to laboratory variables were reported.

Two subjects had a total of 2 AEs during the study. Both of the events were considered by the investigator to be possibly related to the study medication and both were considered to be mild in intensity

Table 10: Summary of Adverse Events

Subject Number	Preferred Term	Fed/Fast	Relationship	Intensity
03	Dizziness	Fed	Possible	Mild
16	Throat Irritation	Fed	Possible	Mild

Both dizziness and throat irritation occurred at a % incidence of 5.3%.

No AEs related to laboratory variables were reported, all results outside the normal reference range were assessed as not clinically significant by the investigator or repeated.

Pulse rate and blood pressure remained essentially unchanged throughout the study. Body temperature before dosing on clinic days ranged between 35.6°C and 37.1°C, and no subjects were withdrawn due to pathologically raised body temperature.

12-lead ECGs were performed on all subjects. One abnormal 12-lead ECG result was reported (QTc >450 ms [QTcF = 434.3 ms]) but was considered by the investigator to be not clinically significant. No abnormal 12-lead ECG results were reported for any of the other subjects.

No clinically relevant abnormalities were observed in any of the subjects for the physical examinations performed at screening. One abnormal physical examination was reported (strabism) but was considered by the investigator to be not clinically significant.

No abnormal results were reported or the slit lamp eye examinations performed during screening and at post-study.

Study CT-001

No deaths or SAEs were reported during the study and no AE was of severe intensity. One subject (a 24 year old, male subject) with no notable medical history vomited from 12:11 to 12:12. The investigator reported it as an AE and the subject was withdrawn from the study on 26 October 2015 as he vomited before 2 times median Tmax. The AE was considered by the investigator as possibly related to the IMP and to be mild in intensity.

Ten of the 24 subjects reported 14 TEAEs. Nine TEAEs were considered by the investigator to be possibly related to the IMPs (Reference Product: 5 AEs; Test Product 1: 1 AE; Test Product 2: 3 AEs). The adverse events were mild in intensity.

There was no clinically significant and/or consistent drug-related change in vital signs, physical findings or safety laboratory values after administration of a total dose of 10 mg nitisinone per treatment period.

Generally the safety data is in line with that of the reference product although an extra patient experienced pruritus with test product 2 versus Test product 1 or reference however this could be a chance finding as the numbers are too low.

Conclusions on pharmacokinetics

Bioequivalence was demonstrated in Study CT-003 and based on the PK parameters of nitisinone 10 mg tablets (Test product 1) compared with Orfadin® 10 mg hard capsules (Reference).

- For Cmax the mean ratio was 95.90% with the 90% confidence interval between 91.66% and 100.34%.
- The mean ratio of AUC(0-72) was 98.81% with confidence interval between 95.63% and 102.09%.
- The mean ratio of AUC(0-120) was 99.86% with confidence interval between 96.34% and 103.51%.
- The tmax was 2.50 hours and 3.5 hours for the reference and the test product, respectively, and was not statistically different between the 2 products.

In addition, bioequivalence was based on the PK parameters of nitisinone 10 mg tablets (6 months @ 40°C/75% RH) (Test Product 2) compared with Orfadin® 10 mg hard capsules (Reference).

For Cmax the mean ratio was 95.55% with the 90% confidence interval between 91.14% and 100.19%.

The mean ratio of the AUC(0-72) was 98.05% with confidence interval between 93.98% and 102.28%.

The mean ratio of AUC(0-120) was 98.84% with confidence interval between 94.75% and 103.11%.

The tmax was 2.50 hours and 3.90 hours for the reference and the test product, respectively, and was statistically different between the 2 products. Bioequivalence has been shown in Study CT-003 between Test Product 1 and 2 and the reference product according to standards set by Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)

Regarding the fast/fed study CT-002, the point estimates of the "Fed/Fast" mean ratios of the PK parameters Cmax, AUC(0-72) and AUC(0-120) for nitisinone are 91.11%, 95.07% and 95.30%, respectively.

The 90% CI for the "Fed/Fast" mean ratios of the PK parameters Cmax, AUC(0-72), and AUC(0-120) for nitisinone are 86.56% to 95.91%. 92.70% to 97.50%, and 92.71% to 97.95%, respectively.

Basing bioavailability on Cmax and AUC(0-72), Nityr has been shown to be bioequivalent in fasting and fed states, the fed state reduced the subject variability.

Under the fed state, the AUC(0-120) coefficient of variation was reduced from 26.4 (fasted) to 17.1%. Under the fed state, the AUC(0-72) coefficient of variation was reduced from 25.0% (fasted) to 16.8%. The median Tmax was 6.0 hours and 3.0 hours for the fed and the fast, respectively, and was statistically different between the study conditions (p=0.0048).

Regarding the supportive study CT-001, for test product 1 The point estimates of the "test/reference" mean ratios of the PK parameters Cmax, AUC(0-72) and AUC(0-120) for nitisinone are 97.80%, 100.43% and, 100.83% respectively.

The 90% confidence intervals for the "test/reference" mean ratios of the parameters Cmax, AUC(0-72) and AUC(0-120) for nitisinone are 93.77% to 102.00%, 96.84% to 104.15% and 96.58% to 105.27% respectively

For Test product 2: The point estimates of the "test/reference" mean ratios of the parameters Cmax ., AUC(0-72) and AUC(0-120) for nitisinone are 92.95%, 94.32% and 94.22%, respectively.

The 90% confidence intervals for the "test/reference" mean ratios of the parameters Cmax., AUC(0-72) and AUC(0-120) for nitisinone are 84.03% to 102.82%, 84.58% to 105.19% and 84.85% to 104.63%, respectively. Bioequivalence for both test products has been demonstrated.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available.

2.4.5. Discussion on clinical aspects

Nitisinone should be administered with a tyrosine and phenylalanine restriction diet. There is a predictable increase in plasma tyrosine concentrations if nitisinone is administered without a restricted diet.

To support the application, the applicant conducted 3 bioequivalence studies.

Pharmacokinetic and bioequivalence study summary for Nitisinone Cycle

Study type	Study number	Study design	Subject number	IMP*	Results
Pivotal bioequivalence study	CT-003	3-way crossover, 3-period, 3-treatment bioequivalence study	23	ORFADIN capsules 10 mg Nitisinone Cycle tablets 10 mg Aged Nitisinone Cycle tablets 10 mg	Bioequivalence was established between ORFADIN capsules and both Nitisinone tablets formulations.
Pivotal food effect study	CT-002	2-way crossover, 2-period food effect study	19	Nitisinone tablets 10 mg	No statistical difference between the pharmacokinetic of Nitisinone tablets administered under fasted and fed conditions.
Pharmacokinetic study	CT-001	3-way crossover, 3-period, 3-treatment bioequivalence study	23	ORFADIN capsules 10 mg Nitisinone Cycle tablets 10 mg High Compritol Nitisinone Cycle tablets 10 mg	Bioequivalence was established between ORFADIN capsules and both Nitisinone tablets formulations.

All 3 studies examined for BE-using the 10mg dose with results meeting the predefined limits, in line with the respective EMA Guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

All of the studies were reported to be in line with GCP and had ethical approval in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted.

CT-001 was a 3-way cross-over study single dose in fasting state. There were 2 test products 10mg and a 10mg tablet with a higher compritol level.

CT-002 study examined the 10mg test product in fasting and fed conditions.

CT-003 study was the pivotal bioequivalence study and similar to the other studies and examined 10mg test product, 10mg aged test product to the reference in fasting conditions again bioequivalence was demonstrated.

All of the studies were sufficiently powered for, the applicant accounted for the patients enrolled and the protocol deviations that occurred were detailed. These were not deemed to be significant as they were unlikely to affect the bioequivalence conclusions of the trials. The statistical methods of analyses were similar and acceptable.

The bioanalytical analyses were also similar between the studies and were also found to be acceptable.

All the treatments were administered as single 10 mg doses of Nitisinone with a washout of at least 23 days between each treatment period. Pharmacokinetic samples were collected over 120 hours in each treatment period.

Pharmacokinetic samples were collected over 120 hours in each treatment period. The PK parameters were calculated with non-compartmental methods, and Cmax and AUC0-120 were analysed.

The results demonstrated that for all test products bioequivalence was demonstrated between Nityr (test product 1 and test product 2) and ORFADIN capsules (reference product) as the 90% confidence intervals of both PK parameters are within 80% and 125%.

Additionally, a food effect study (CT-002) was conducted with the Nityr tablets 10 mg (batch 151159) to investigate the food effect on the bioavailability of Nityr tablets. Nityr was administered as single 10 mg doses of nitisinone with high fat food under fed conditions, with a washout of at least 23 days between each treatment period. Pharmacokinetic samples were collected over 120 hours in each treatment period. The PK parameters were calculated with non-compartmental methods, and Cmax and AUC0-120 were analysed. Bioequivalence was demonstrated between the Nityr administered under fasted and fed conditions, suggesting that there is no food effect for Nityr.

A biowaiver was sought for the lower strengths (2 mg and 5 mg). The justification presented by the applicant to deviate from the requirements of the guideline on investigation of bioequivalence for a biowaiver for the lower strengths (2mg and 5mg) was not accepted by the CHMP in consultation with the PKWP. The applicant subsequently withdrew the application for the 2 mg and 5 mg strengths.

Infant administration

To support the administration in paediatric patients or patients who are not able to swallow the tablets, alternate delivery methods were proposed for Nityr tablets

However, it was agreed that instead a statement would be included in the SmPC stating that for such patients, other pharmaceutical forms are available.

The following statement was added to the SmPC and package leaflet:

SmPC: *For paediatric patients who have difficulties swallowing tablets, other pharmaceutical forms are available.*

Package Leaflet: *Patients who have problems swallowing NITYR tablets whole, including children, are recommended to take alternative nitisinone formulations.*

Safety

The safety evaluations, clinical laboratory evaluations, vital signs, ECG and physical exam results provided are consistent with the reference product and no new safety concerns were reported.

The pre- and post-marketing safety data collected for ORFADIN capsules are limited. This reflects the worldwide rarity of patients with HT-1. The safety data relating to nitisinone are located in the NTBC Study (main and complimentary), published literature and post-marketing experience for ORFADIN capsules (PSURs). Data from the bioequivalence and food-effect studies conducted by Cycle Pharmaceuticals did not impact on the safety profile of nitisinone.

The safety data extracted from the literature are generally consistent with that found in the NTBC Studies (main and complimentary analysis). Reports extracted from the literature and the Bridging PSUR included a number of adverse events associated to neurological disorders such as impaired cognitive function and development problems which were not recorded in the NTBC Studies. However, such developmental problems have been associated with high tyrosine levels, which are already closely monitored and controlled in HT-1 patients receiving nitisinone.

The most common AEs related to nitisinone treatment (ARs) are visual disorders, which in the majority are found to be non-serious and disappear either spontaneously or after improved compliance with the diet. Besides eye symptoms, the adverse events, which may be attributed to treatment with nitisinone include thrombocytopenia and leucopenia and skin symptoms.

As this is a generic application, the demonstration of bioequivalence can support bridging to the efficacy and safety of the reference product ORFADIN capsules.

No deaths or SAEs were reported during the study and no AE was of severe intensity, the adverse events which occurred in the clinical program were mild to moderate in nature.

The applicant did not conduct additional safety or efficacy data which is acceptable for this application.

However, due to the limited number of patients with sufficient follow-up, the long-term safety profile of nitisinone is not well-known, the applicant will continue to closely monitor all safety data.

Based on the presented bioequivalence studies provided, Nityr 10mg tablets is considered bioequivalent with ORFADIN 10mg capsules.

2.4.6. Conclusions on clinical aspects

The one pivotal and two supportive studies showed bioequivalence between the reference 10mg capsules and the applicant's 10mg tablet formulations. These supported several aspects of the Nitisinone Cycle application. Firstly in CT-003 it has been shown that the 10mg dose meets the predefined limits, in line with the respective EMA Guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) for bioequivalence and bridging the CHMP's previous findings on efficacy and safety of ORFADIN capsules can be accepted for this formulation.

CT-002 displayed bioequivalence in the fasting and fed state and supports the administration of tablets with food.

CT-001 displayed bioequivalence between the 10mg reference and test products and a modified formulation of Nityr tablets with a higher Compritol 888 content however the stability of aged Nityr (stored at 40°C/75% RH for more than 6 months) was explored better in the pivotal study.

The justification for a biowaiver for the 2 mg and 5 mg strengths was not accepted and the applicant has withdrawn the 2mg and 5mg tablets for marketing authorisation and therefore authorisation for the 10mg tablet strength only is accepted. The product information has also been updated accordingly to reflect this.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	Increased tyrosine levels Hypertyrosinemia related eye disorders Leukopenia/Granulocytopenia
Important potential risks	Developmental and cognitive disorders Use in AKU patients (Off label) Embryo-foetal toxicity Exposure to nitisinone during breast-feeding Lack of efficacy
Missing information	Interaction with inducers and inhibitors of CYP3A4 Use in elderly HT-1 patients Use in pregnancy Once daily administration Carcinogenic potential

Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] category 1-3)	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Post-approval surveillance study (PASS)/ Nitisinone Tablets for Hereditary Tyrosinemia type 1 (HT-1) in Canada Category 3	To evaluate the long-term safety of Nitisinone tablets in the treatment of HT-1 and monitor its safety profile during pregnancy	Long-term safety of Nitisinone tablets and to monitor its safety profile during pregnancy.	Planned	Planned Interim update (if the study is started) to be included in ASR to Health Canada in December 2019

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Increased Tyrosine Levels	Routine Pharmacovigilance	None Proposed
Hypertyrosinemia related eye disorders	Routine Pharmacovigilance	None Proposed
Leucopenia /Granulocytopenia	Routine Pharmacovigilance	None Proposed
Developmental and cognitive disorders	Routine Pharmacovigilance	None Proposed
Exposure to nitisinone during breast-feeding	Routine Pharmacovigilance	None Proposed
Use in pregnancy	Routine Pharmacovigilance	None Proposed
Use in elderly HT-1 patients	Routine Pharmacovigilance	None Proposed
Use in AKU patients (off label use)	Routine Pharmacovigilance	None proposed
Interaction with inducers and inhibitors of CYP3A4	Routine Pharmacovigilance	None Proposed
Embryo-foetal toxicity	Routine Pharmacovigilance	None Proposed
Lack of efficacy	Routine Pharmacovigilance	None Proposed
Carcinogenic potential	Routine Pharmacovigilance	None Proposed
Once daily administration	Routine Pharmacovigilance	None Proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Orfadin capsules. The bridging report submitted by the applicant has been found acceptable.

2.7.2. Labelling exemptions

A request to omit certain particulars from the immediate label (bottle label above 10 ml) has been submitted by the applicant and has been found acceptable by the QRD Group because of space constraint (especially for the multilingual label).

The particulars agreed to be printed on the bottle label are: Invented name, strength, pharmaceutical form, INN, route of administration, 'contains lactose', MAH, EXP and Lot, special storage condition, shelf-life after first opening and content by unit.

3. Benefit-risk balance

This application concerns a generic version of nitisinone tablets. The reference product Orfadin is indicated for treatment of Hereditary Tyrosinemia Type 1.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a cross over design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling times as well as wash-out period were

adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were also adequate.

The test formulation of 10 mg Nityr applied product met the protocol-defined criteria for bioequivalence when compared with the 10mg Orfadin capsule formulation reference product. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞ and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded for the 10 mg strength tablet of Nityr.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nityr 10 mg is favourable in the following indication:

Treatment of adult and paediatric patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

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.

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.

Additional risk minimisation measures

Not applicable.

Obligation to conduct post-authorisation measures

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.