EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
EMA/389927/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orfadin

International non-proprietary name: nitisinone

Procedure No. EMEA/H/C/000555/X/0041

Note

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

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List of abbreviations

AE	Adverse event
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANOVA	Analysis of variance
APL	Apotek Produktion & Laboratorier
ASAT	Aspartate aminotransferase
AUC72h	Area under the serum concentration-time curve from time 0 to72 hours postdose
AUCinf	Area under the serum concentration-time curve from 0 to infinity
BMI	Body mass index
CHD	1,3-cyclohexanedione
CI	Confidence Interval
CL/F	Apparent total body clearance after oral administration
Cmax	Maximum observed serum concentration
CRO	Contract research organization
CSP	Clinical Study Protocol
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
FDA	Food and Drug Administration
γ-GT	Gamma-glutamyltransferase
GCP	Good clinical practice
HBsAg	Hepatitis B surface antigen
HepC	Hepatitis C
HIV	Human immunodeficiency virus
HT-1	Hereditary tyrosinemia type 1
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
k(el)	Terminal elimination rate constant
LC/MS	Liquid chromatography/mass spectrometry
LDH	Lactate dehydrogenase
LOCF	Last-observation-carried-forward
LLOQ	Lower limit of quantitation
MCH	Mean hemoglobin concentration
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
NCA	Noncompartmental analysis
PIP	Pediatric investigational plan
PK	Pharmacokinetics

PPS	Per protocol set
PPSBE	Per protocol set for bioequivalence
PPSFE	Per protocol set for food effect
PT	Preferred term
PPAS	Per-protocol analysis set
QSAR	Quantitative Structure-Activity Relationship
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
t½	Terminal half-life
tmax	Time at which the maximum serum concentration is observed
Vz/F	Apparent volume of distribution during the terminal phase

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Swedish Orphan Biovitrum International AB submitted on 31 July 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Orfadin 4 mg/ml oral suspension, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 intend d) of the Commission Regulation (EC) No 1234/2008.

Swedish Orphan Biovitrum International AB is already the Marketing Authorisation Holder for Orfadin 2mg, 5 mg and 10 mg hard capsules (EU/1/04/303/001-003).

The MAH applied for a line extension to include a new pharmaceutical form of 4 mg/ml oral suspension, 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 legal basis for this application refers to:

The application submitted is composed of administrative information, complete quality data and at least a bioequivalence study.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0065/2012 on the agreement of a paediatric investigation plan (PIP).

The PIP P/0276/2013 was completed. The PDCO issued an opinion on compliance for the PIP P/0276/2013.

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.

1.2. Manufacturers

Manufacturer responsible for batch release

Apotek Produktion & Laboratorier AB
Celsiusgatan 43
Malmö
20120
Sweden

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Luca Pani

- The application was received by the EMA on 31 July 2013.

- The procedure started on 21 August 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 November 2013.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 5 December 2013.
- During the meeting on 19 December 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 December 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 October 2014.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 9 October 2014.
- During the CHMP meeting on 23 October 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 March 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 April 2015.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 10 April 2015.
- During the meeting on 23 April 2015, 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 Orfadin 4 mg/ml oral suspension.

2. Scientific discussion

2.1. Introduction

Orfadin is the only available pharmacological treatment option for HT-1. Infants and children represent the majority of patients currently treated with Orfadin. The treatment is life-long and should be initiated as early as a couple of weeks after birth. Even if the target population are paediatric patients, the only and currently approved formulation for Orfadin is hard gelatin capsules provided in 3 strengths (2 mg, 5 mg and 10 mg). The recommended initial daily dose is 1 mg/kg. A limit of the capsule formulation is that the youngest patients are unable to swallow them, and for that reason the capsules have to be opened and the contents mixed with food or drink, which may be leading to inaccurate dosing. The capsules are thus not an optimal dosage form for infants and children. For that reason, during the approval process of Orfadin (EMEA/H/C/555) the CHMP expressed the need for an age appropriate pediatric formulation. The company's position at that time was that the number of new patients diagnosed would have been very small. Nevertheless, the company has revisited this decision. Extended newborn screening which is becoming more common in Europe has increased the number of identified newborn HT-1 patients. As a consequence, patients are identified earlier. Especially these newborn patients would benefit from a liquid formulation, which would enable more

exact dosing. Therefore, the company has concurred with the CHMP request to develop a liquid formulation, an oral suspension (4 mg/mL).

Orfadin suspension was developed to facilitate the ease and accuracy in administration of the desired Orfadin dose to paediatric patients, and to increase convenience for the patients and their parents/caregivers.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as new oral suspension containing 4 mg/ml of nitisinone as active substance.

Other ingredients are: hydroxypropyl methylcellulose, glycerol, polysorbate 80 , sodium benzoate, citric acid monohydrate, trisodium citrate dihydrate, strawberry aroma, water purified.

The product is available in a brown bottle (type III glass) with a white child resistant HDPE cap with sealing and tamper evidence. It is provided with a low density polyethylene (LDPE) oral syringe adaptor to be inserted in the bottle neck and a set of three polypropylene (PP) oral dosing syringes of different sizes and graduations: 1.00, 3.0 and 5 ml.

2.2.2. Active Substance

General information

The active substance nitisinone, used to manufacture the new pharmaceutical form, oral suspension 4mg/ml, is the same as that used in the manufacture of the currently registered Orfadin hard capsules 2 mg, 5 mg, 10 mg. For the manufacture of the oral suspension, after release of the active substance, micronisation is performed to reduce the particle size in order to favour its suspendibility. Finished Medicinal Product

Description of the product and pharmaceutical development

The new oral suspension formulation is intended to make administration of Orfadin to infants and children easier and more accurate. It is primarily aimed for neonates, infants and children, representing a body weight span of approximately 3.5 to 40 kg. A daily dose of 1 mg nitisinone/kg thus corresponds to a dose range from 1.75 mg to 20 mg administered twice daily. The strength of 4 mg/ml for the oral suspension was chosen in order to achieve acceptable dosage volumes corresponding to 0.4 ml to 5 ml administered twice daily.

Previous attempts to develop an aqueous liquid formulation of Orfadin were not successful due to stability problems and therefore a suspension was developed. For the purpose of developing a suspension the active substance is micronised in order to favour the suspendibility of the active substance and to maintain the homogeneity of the suspension during the time it takes to measure the dose. The influence of particle size on the active substance dissolution has been investigated. The discriminatory power of the dissolution method has been demonstrated. However, the CHMP recommended that the specification acceptance criterion of the dissolution test should be re-assessed after the production of the 10 first commercial batches.

The proposed excipients used in Orfadin oral suspension were chosen based on the extensive experience generated by the use of these excipients in a wide range of pharmaceutical preparations including formulations for children and infants. All the chosen excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. The preservative effectiveness of the current formulation was optimized according to Ph. Eur. 5.1.3 using different levels of sodium benzoate. The flavouring complies with the provisions of EU Regulation No. 1334/2008 on flavourings and certain food ingredients with flavouring properties for use in or on

foods. Furthermore, all of the flavouring ingredients used in this strawberry aroma product are listed as GRAS (Generally Recognized As Safe) by the Flavor and Extract Manufacturers Association (FEMA) and/or are approved in accordance with the US Code of Federal Regulations. The amount of excipients was kept as low as possible and does not differ from what have been used previously in other medicinal products intended to be used in children and infants. The oral route of administration is the most common route where these excipients have been exploited and is also the safest regarding the limited oral bioavailability of the excipients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Uniformity of mass of delivered doses from multidose containers (Ph. Eur. 2.9.27) and content uniformity of delivered dose (Ph. Eur. 2.9.40) was investigated in order to establish the dose accuracy.

A bioequivalence study was performed showing bioequivalence between the commercial 10 mg capsule with the oral suspension, 4 mg/ml.

A standard brown type III glass bottle is chosen as primary container. The bottle is sealed with a white child resistant HDPE (high density polyethylene) cap with sealing and tamper evidence. The cap materials in direct contact with the pharmaceutical product consist of LDPE with additives and are described in Ph. Eur. The administration devices, i.e. the three oral syringes and an oral syringe adaptor, are CE marked. The sizes and graduation of the three oral syringes, have been chosen to cover appropriate dosing in the intended age group, i.e. for newborn infants up to children 8-10 years of age.

Compatibility with the container closure was studied storing the bottles inverted as part of the formal stability studies in one batch followed by storing the corresponding samples in an up-right position at 40 ºC for 6 months.

Manufacture of the product and process controls

The manufacturing process consists of 6 main steps: micronisation of active substance, mixing of ingredients, filling into glass bottles, capping, labelling and packaging. 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 pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC with UV detection), related substance (HPLC with UV detection), pH (Ph Eur), sodium benzoate (HPLC with UV detection), uniformity of mass of delivered doses from multidose containers (Ph Eur), assay (HPLC with UV detection), dissolution (Ph Eur), microbiological quality (Ph Eur), and specified microorganisms (Ph Eur).

The test for resuspendability is performed as part of the European Pharmacopoeia method 2.9.27 “Uniformity of mass of delivered doses from multidose containers”.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The CHMP recommended to re-assess the limits of the impurities, of nitisinone assay at shelf-life and of sodium benzoate assay at release and shelf-life after the production of the 10 first commercial batches.

Stability of the product

Stability data of 3 production scale batches of finished product stored under long term conditions for 24 months at 5 ºC / ambient RH, and 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of the

medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, related substance, pH, antimicrobial preservative, uniformity of mass, assay, microbiological quality and particle size. The analytical procedures used are stability indicating.

A photostability study on two batches of finished product was conducted according to ICH Q1B. The results showed that Orfadin oral suspension was not light sensitive and can therefore be stored unprotected from light during use.

A temperature cycling (freeze-thaw) study between -20 ºC and +40 ºC/75 % RH has been conducted to support distribution and transport of refrigerated products. In conclusion neither the chemical nor the physical stability with respect to particle size distribution was affected by the temperature cycling. However, the temperature cycling resulted in an unusually compact cake on the bottom of the bottle and as a consequence an unreasonably long redispersion time (5 minutes) prior to first opening as compared to the minimum of 20 seconds prescribed in the instructions for use of the product. The content of nitisinone was very low in one of the bottles after temperature cycling. This is probably due to the fact that the appearance of the suspension and the time for redispersion were affected by the temperature cycling. Based on this the drug product should not be subjected to freezing conditions and a warning text “Do not freeze” has been included in the label of the product.

Two 3 months in-use stability study at ambient room conditions has been conducted on two batches of the finished product stored for 9 and 1 months at +5 ºC prior to start. On each working day a 0.5 ml dose was withdrawn in the morning and afternoon with the 1 ml oral syringe, weighed and the mass variation evaluated according to Ph. Eur. 2.9.27. Between each dosing the suspension was redispersed by gentle turning of the bottle up and down 30 times. The same oral syringe was used throughout the whole study and it was rinsed with water between each dosing. After the completion of the study the test according to Ph. Eur. 2.9.27 was performed in order to investigate the performance of the oral syringes after the 3 months use period. Tests for appearance, assay, purity and pH were performed monthly and test for microbiological quality on the remaining product after completion of the study. In addition, a confirmatory study at end of shelf life (22 months) was performed.

In addition an in-use stability study of hold time and a photostability study with the product withdrawn in the syringe at the temperature NMT 25 ºC to investigate the compatibility and stability (in-use, photostability) of the product withdrawn in the syringe have been performed. The results supported the immediate use of the dose withdrawn in the syringe.

The results obtained from the formal stability studies and the in-use stability studies were within specification. Considering also the instruction in the product information that the oral suspension should be administered immediately after withdrawal into the oral syringe, the proposed shelf-life can be considered acceptable.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.3. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The new oral suspension formulation is intended for paediatric population and has been demonstrated to ensure easier and more accurate dosing. The

excipients are considered acceptable with regard to the intended population. 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.

2.2.4. 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.

2.2.5. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-To re-asses the limit of the dissolution test (75% to 30 min) after the production of the 10 first commercial batches.

- To re-assess the limits of the impurities, of nitisinone assay at shelf-life and of sodium benzoate assay at release and shelf-life after the production of the 10 first commercial batches.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

N/A

2.3.3. Pharmacokinetics

N/A

2.3.4. Toxicology

The applicant submitted report **TKT-2013-007 Computational assisted prediction of Genotoxicity.** The potential bacterial mutagenicity of six compounds: nitisinone, OTHX, CHD, TSA, NTPDHA, and the starting material 2-nitro-4-(trifluoromethyl)benzoic acid, was predicted by two (Q)SAR prediction methodologies complementing each other: Derek Nexus (an expert-knowledge based toxicity prediction tool) and Leadscope Model Applier (a statistical-based prediction tool).

Further to CHMP request, the Applicant performed a bacterial mutagenicity test of NTPDHA , a degradation product in Orfadin oral suspension, and OTHX which is only formed in Orfadin oral suspension at exaggerated storage conditions (+40 °C) and not at normal (+5 °C) or accelerated (+25 °C) conditions. The submitted studies and relevant findings are shown below:

Type of study	Species/strain	Method of administration	Doses	Noteworthy findings
Study UJP0002 no GLP Ames Test	S.typhi/TA1535, TA1537, TA98, TA100 E. coli / WP2P uvrA	In vitro	0, 50, 150, 500, 1500, 5000 µg/plate	No dose-related or statistically significant increases in revertant numbers observed in any strain at any dose of OTHX, in the presence or absence of S9, under plate incorporation conditions.
Study UJP0001 no GLP Ames Test	S.typhi/TA1535, TA1537, TA98, TA100 E. coli / WP2P uvrA	In vitro	0, 50, 150, 500, 1500, 2500, 3500, 5000 µg/plate	There was a dose related, statistically significant increase in revertant colonies in TA100 in the absence of S9 at 500, 1500 and 5000 µg/plate. There was a similar dose related, statistically significant increase in revertant colonies in TA100 in the presence of S9 at 3500 and 5000 µg/plate.
Study 8302339 GLP Ames Test	S.typhi / TA100, TA100NR	In vitro	5-5000 µg/plate	The increases in revertant numbers observed following treatments of the nitroreductase deficient strain TA100NR were smaller than the responses occurring in the parent strain at equivalent test concentrations (5000 µg/plate)
Study 8302340 GLP Mouse Micronucleus and Alkaline Comet Assay	Mouse/CD-1	Oral gavage 3 days administration	350, 700, 1400 mg/kg	NTPDHA induced micronuclei in the polychromatic erythrocytes of the bone marrow in male mice treated at 700 and 1400 mg/kg/day under the experimental conditions employed. Comet Assay results indicate that NTPDHA did not induce DNA damage in the liver, duodenum or blood of male mice treated up to 1400 mg/kg/day (an estimate of the maximum tolerated dose for this study). FISH-analysis of the induced micronuclei revealed that the chromosomal lesions were mediated by a clastogenic mechanism, i.e. the majority of the induced micronuclei were centromere-negative

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as Orfadin is a rare inborn error of metabolism, and is the only approved medicinal product for this orphan disease. The use of nitisinone, and consequenty the concentration in the environment, will thus not increase as

the oral suspension will merely replace use of the capsules for some patients who have difficulty to swallow.

Thus, the environmental risk from this line-extension is expected to remain similar as before, and not increased.

2.3.6. Discussion on non-clinical aspects

The genotoxicity evaluation of OTHX and NTPDHA was taken into consideration, in order to further demonstrate the positive prediction for bacterial mutagenicity detected by means of (Q)SAR-analysis.

OTHX was shown not to be potentially mutagenic in the Ames test, therefore was considered as a non-genotoxic impurity, according to the ICH Q3B guideline recommendations.

When NTPDHA was subjected to a bacterial reverse mutation test, weak mutagenic responses were observed both in the absence and in the presence of metabolic activation. Moreover, to demonstrate the involvement of nitro-reductase in the activation of NTPDHA, two strains of TA100 (with and without nitroreductase) were assessed, in absence of metabolic activation. NTPDHA tested negative in the nitro-reductase deficient TA100NR strain. The increases in revertant numbers observed following treatments of the nitroreductase deficient strain TA100NR were smaller than the responses occurring in the parent strain at equivalent test concentrations. This suggested that bacterial nitroreductase enzyme plays a role in the mutagenic response seen with NTPDHA in the parent strain TA100.

In order to understand the in vivo relevance of the in vitro mutagenicity test results, the genotoxicity of NTPDHA was further investigated in mice.

Administration of NTPDHA at higher doses resulted in increased frequencies of micronucleated polychromatic erythrocytes (PCE) in the bone marrow of mice. The results suggest the identification of NTPDHA as a weak bacterial mutagen, even though the effects on the mouse micronuclei did not lead to DNA damage in liver and blood as shown by Comet Assay. They seem not to be linked, according to the Applicant, to the nitro-reductase dependent bacterial mutation results. Moreover, the chromosomal lesions were mediated by a clastogenic mechanism, as revealed by FISH test.

A practical threshold for the genotoxicity of NTPDHA was defined as the NOEL/NOGEL in the mice study, i.e. 350 mg/kg. According to the EMEA/CHMP/QWP/251344/2006 guidance on genotoxic impurities, the PDE for this genotoxic impurity was calculated for the different paediatric populations.

The Applicant adequately addressed a request from CHMP to clarify the way the body weights were extrapolated for the PDE calculation. The calculated PDE for each patient age category was indeed based on the lowest body weight expected in that cohort (3rd percentile in the WHO growth chart in children at the age of 0 to 5 years, gender average), thus the lower the PDE the more conservative will the risk assessment of the impurity become.

2.3.7. Conclusion on the non-clinical aspects

Satisfactory responses were given by the Applicant with regards to the Questions raised regarding the non-clinical aspects.

2.4. Clinical aspects

2.4.1. Introduction

To support this MAA, the applicant has submitted one bioequivalence study (Sobi.NTBC-001) and a taste and palatability study (Sobi.NTBC-002).

No new clinical studies were submitted

Summary of biopharmaceutic studies

Study nr	Study objectives	Study design	Treatments	Subjects	Main variables
Sobi.NTBC-001 (Netherlands)	To assess bioequivalence between nitisinone oral suspension and nitisinone capsules; effect of food on the bioavailability of nitisinone oral suspension; safety	Open, randomized, 3-way crossover study, single-center study	Orfadin suspension containing 4 mg/mL nitisinone: Dose: 30 mg (7.5 mL), oral. Batch number: 3014653 Orfadin capsule, containing 10 mg nitisinone: Dose 30 mg (3 capsules), oral. Batch number: 3012535	Healthy male volunteers, aged 18-55 years (inclusive). n=12	AUC_{72h} and C_{max} (suspension and capsules under fasting conditions, suspension with food), t_{max}, safety assessments
Sobi.NTBC-002 (UK, Germany, France)	To assess acceptability of the oral suspension in the pediatric population; safety	Open, non-randomized, non-controlled, multi-center study	Orfadin suspension containing 4 mg/mL nitisinone; Dose as determined by the investigator based on each patient's current prescribed dose, oral. Batch number: 3015416	Pediatric patients diagnosed with HT-1, aged 1 month to <18 years. n=18	Patient questionnaire data on taste, palatability and acceptability, safety assessments

AUC_{72h} = the area under the serum concentration vs. time profile curve during 72 hours after dose; C_{max} = the maximum serum concentration; HT-1 = hereditary tyrosinemia type 1; t_{max} = time to reach C_{max}; UK = United Kingdom

2.4.2. Pharmacokinetics

Study Sobi.NTBC-001 was a study to evaluate the bioequivalence of Orfadin suspension 4mg/ml compared to Orfadin capsules 10 mg, and the effect of food on the bioavailability of the suspension.

The aim of this study was to demonstrate bioequivalence between the new Orfadin oral suspension and the marketed capsule formulation and also to analyze the effect of food on the new formulation. This study was part of the agreed PIP.

Study design: This was an open label, randomized, 3-way cross-over, single-dose bioequivalence study in 12 healthy volunteers. The study was designed according to the recommendation of the guideline on the investigation of Bioequivalence.

The primary objective of this study was to show bioequivalence between nitisinone oral suspension and nitisinone capsules and endpoints related to this objective were the AUC0-72h and the Cmax, both under fasting conditions. The secondary objectives were: i) to assess the food effect on the BA of nitisinone oral suspension; ii) to assess selected PK variables for nitisinone capsules and suspension, the latter given with and without food, at a single oral dose of 30 mg; and iii) to assess the tolerability and safety of nitisinone capsules and suspension, the latter given with and without food, after single oral doses of 30 mg.

In order to obtain a correct characterization of the PK profile of nitisinone, venous blood samples were drawn in 3.5 ml tubes containing a clot activator and gel barrier at baseline (pre dose) and at the following times: on Day 1 pre-dose and at 15, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours post-dose.

The wash-out period of 2 weeks is considered adequate since the drug has a half-life of about 54 hours and pre-dose levels were not detected at the beginning of the second period. Time to peak concentration is expected to be reached in about 4 hours (in fasting conditions) and, taking into account the elimination half-life of nitisinone, the sampling schedule and the sampling time period of 72 hours seem adequate to estimate PK parameters and PK profile of nitisinone.

Test and reference products: The test product was the Orfadin oral suspension containing 4 mg/mL of nitisinone. The test and reference products are adequate for a line extension application. The dose of 30 mg (approx. 0.3 to 0.5 mg/kg) was selected to have a serum concentration sufficient to be measured in all samples.

Subjects fasted from at least 10 hours before dosing, except for the period when they took the IMP after breakfast. When nitisinone was administered under fasting conditions (in 2 of the 3 periods), no food was allowed until lunch, 4 hours after drug administration. In one period the suspension was administered 30 minutes after the start of a high-fat breakfast, which had to be eaten within no more than 20 minutes. The composition of the meal is according with the requirements of the Guideline on the investigation of bioequivalence.

Population studied: As planned, a total of 12 Healthy volunteers were included in the study and analyzed, which is considered adequate to show equivalence based on data from a previous bioequivalence study. The subjects, considered acceptable with regards to demographic characteristics, were male, 18 to 55 years of age with a body mass index (BMI) of 18.5 to 30.0 kg/m2 (inclusive). The inclusion and exclusion criteria were acceptable. No subjects was withdrawn from the study. None of the deviations described above was judged to affect the study results or subject safety.

Analytical methods: Quantitative analyses of nitisinone in the individual serum samples, as well as in suitable quality control samples, were performed using a validated liquid chromatography/mass spectrometry (LC/MS/MS) method.

A total of 684 samples were analysed. All calibration standards utilised within the regression had back calculated values that were within the acceptance criteria as stated in the protocol. The QC sample data in each reported analytical run were within the acceptance criteria as stated in the protocol. The inter-day precision (relative standard deviation, RSD%), using spiked human serum samples was below 3.9 %. The inter-day accuracy, expressed as % of nominal value, ranged from 98.5 to 102 %. The method did pass the incurred sample reproducibility test, a total of 72 samples were included in that test (75 % of the repeated results and original results were within 20 % of each other and within the acceptance criteria).
Chromatograms of calibrant, QC, and subject samples (and corresponding sample sequences) from approximately twenty percent of the subject's chromatograms were presented. The LLOQ is lower than 5% of the minimum Cmax observed and therefore it should be possible to detect eventual carry-over.
Pharmacokinetic variables: Pharmacokinetics variables are appropriate for a single dose bioequivalence study. Bioequivalence was based on AUC72h, due to the long half-life on nitisinone (about 54 hours).

Statistical analysis: The statistical analysis performed is parametric, except for Tmax, in accordance with the Guideline on the investigation on bioequivalence.

Results:
The assessment of bioequivalence complies with the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/Corr**). The 90% confidence intervals for Cmax and AUC0-t fall entirely into the acceptance interval 80.00-125.00%. The assessment of bioequivalence of the Orfadin oral suspension to the Orfadin capsules was based on the AUC72h and on the maximum serum concentration (Cmax) under fasting conditions. Food did not affect the bioavailability of Orfadin suspension, although the absorption under fed conditions is slower than under fasting conditions.

On the basis of these results, bioequivalence between Orfadin oral suspension and Orfadin capsules is considered demonstrated.

Taste, palatability and acceptability

Study NTBC-002

The Applicant performed the Study Sobi.NTBC-002, according to what agreed in the approved PIP (EMEA-000784-M01-PIP02-11), in order to verify the taste and palatability of the suspension in the paediatric population.

Study design: This was an open, non-randomized, non-controlled, multiple-dose, multiple-center study in paediatric patients diagnosed with hereditary tyrosinemia type 1 (HT-1).

A total of 18 subjects were planned to be included, with 6 subjects each in the following age groups: 1 month to <2 years, 2 years to <12 years and 12 years to <18 years. Even if the target population of the oral suspension will be very probably represented by those subjects under 12 years of age, or even younger, or those not able to swallow capsules it could be overall agreed, that the choice to include the oldest age category, the adolescents, could add some information.

For data presentation, subjects were divided into 2 age groups: <5 years (n=6) and 5 years to <18 years (n=12).

The primary endpoints were:

- Taste score at the last dose of the suspension on Day 3 for subjects 5 - < 18 years.
- Acceptability score at the last dose of the suspension on Day 3 for subjects < 5 years.

The secondary endpoints were:

- Taste scores on Days 1 and 2 (subjects 5 - < 18 years).
- Acceptability scores on Days 1 and 2 (subjects < 5 years).
- Palatability scores on Days 1, 2 and 3 (subjects 5 - < 18 years).
- Overall acceptability response (subjects 1 month - < 18).
- Adverse events (AEs).

Treatment and dosages: The IMP was Orfadin oral suspension containing 4 mg/mL of nitisinone.
The dosage of the drug was determined based on current prescribed dose. The treatment period was 3 days (twice daily dosing) with a daily dose as current with Orfadin capsules. Administration of Orfadin suspension was given at the same time of the capsule administration, replacing the regular administration of Orfadin capsules during the 3-day treatment period. The Orfadin suspension was always to be administered before (not with or after) a meal, irrespective of how the capsules were normally taken. All use of concomitant medication during the 3-day treatment period was recorded.

All the subjects enrolled in the study were already treated with Orfadin capsules (both patients able to swallow the whole capsules or patients unable, who usually receive Orfadin mixed with food or fluid). Since the objective of the study was not to compare the taste of the suspension with that of the capsules, nor to evaluate different flavours of the suspension, an open, non-randomized design was used, which is considered agreeable. Taste and palatability were evaluated over a period of 3 days (6

doses) which is a very short period, especially considering that Orfadin treatment therapy is life-long and that the patients enrolled in Study Sobi.NTBC-002 were already on Orfadin capsules treatment. In order to mask the slightly bitter taste of the formulation, the applicant decided to use a high concentration of glycerol and to top flavour the product with strawberry aroma. As discussed in EMA relevant Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev.2), "the development of medicinal products with a neutral taste should be considered, especially for medicines used in the treatment of chronic conditions, as strong flavours can become unpalatable with repeated administration".

Assessment of taste, palatability and acceptability: The assessments of taste and palatability were made after administration of the first dose on Day 1 at the clinic, and at home after the evening doses on Days 2 and 3. Subjects who were 5 to < 18 years of age were asked to rate the taste and palatability of the suspension on 5-graded verbal/numerical scales. Parents were instructed to be careful not to influence the child's response. For taste and palatability assessments, the following grading applied: 5 (very good), 4 (good), 3 (neither good nor bad), 2 (bad) and 1 (very bad). For subjects younger than 5 years of age, one of the parents rated the child's acceptability of the suspension on a verbal/numerical scale. For the parental rating of their child's acceptance of the suspension, the following grading applied: 5 (very well), 4 (well), 3 (neither well nor badly), 2 (badly) and 1 (very badly). The overall acceptability was assessed with a Yes/No question after the last dose on Day 3. The method used for assessing taste and palatability for patients aged from 5 to 18 years is agreed, as well as for the patients younger than 5 years of age. Even if validated methods for assessing taste and palatability have not been established, the measurement scale with a facial hedonic 5 points scale is frequently used in that kind of studies and can be considered acceptable.

Statistical plan and sample size: The trial was a descriptive study without any hypothesis testing and therefore no formal sample size calculation was performed.

Results: As planned, a total of 18 subjects were enrolled (7 study centers), 6 for each of the 3 age cohorts. The subjects ages ranged from 0.7 to 15.7 years (mean of 8.03 years). The mean total daily dose of Orfadin suspension was 0.86 mg/kg which was the same as the mean dose prescribed for the capsule. The population can be considered acceptable with regards the demographic characteristics, baseline disease factors and concomitant medications used. No major protocol deviations in the study were reported.

The results show that the majority of the patients aged from 5 to <18 years provided positive, or at least neutral scores for taste and palatability of Orfadin suspension assessed on Day 3. Only one subject reported bad scores. The suspension was acceptable to all patients below 5 years of age, those patients benefiting most from an age appropriate oral suspension. The data obtained at Day 1 and Day 2 for taste and acceptability in both age subsets from 5 to 18 years of age and < 5 years of age are overall comparable to the data obtained at Day 3.

In terms of overall acceptability of the suspension, 4 patients responded that they would not accept taking the suspension again; those patients were aged between 12 and 15 years old, an age range where subjects usually are able to swallow capsules and even prefer to that capsules and not any oral suspension. Three of them had positive or neutral ratings of both taste and palatability, while one of the patients rated the taste and palatability as bad on one occasion.

The Applicant's conclusion that the Orfadin suspension can be considered acceptable in the paediatric population evaluated could be agreed. The study has the minor limitation of the short duration (treatment with the oral suspension for 3 days), justified by the Applicant because the bioequivalence of the suspension and capsule formulations had not been confirmed when the taste/palatability study

was performed; the results presented are useful for the extrapolation on the oral suspension acceptability on the long-term period.

2.4.3. Pharmacodynamics

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

2.4.4. Conclusions on clinical pharmacology

- Orfadin oral suspension is bioequivalent to the capsule formulation when administered under fasting conditions.
- Food does not affect the bioavailability of nitisinone, but absorption under fed conditions is slower than under fasting conditions.
- Based on the presented bioequivalence study, Orfadin oral suspension formulation is considered bioequivalent with Orfadin capsule formulation.
- Study Sobi.NTBC-002 demonstrated that 3 days intake of Orfadin suspension is well accepted in paediatric HT-1 patients aged from 2 months to 18 years old.
- Orfadin suspension was safe and well tolerated in the studies in this MAA; no new or unexpected safety findings in comparison to what has been previously reported for Orfadin capsules have been reported.

2.5. Clinical efficacy

N/A

2.5.1. Discussion on clinical efficacy

N/a

2.5.2. Conclusions on the clinical efficacy

N/A

2.6. Clinical safety

Orfadin capsules have been approved in the US since 2002 and in Europe since 2005 for treatment of HT-1 in combination with dietary restrictions of tyrosine and phenylalanine, in paediatric and adult patients.

The Applicant declares that presently, approximately 850 patients are treated with Orfadin capsules worldwide. The majority of those patients currently treated with Orfadin are infants and children.

Safety information from the clinical studies with Orfadin capsules has been reported to EMA in the initial application for the approval of Orfadin (EMEA/H/C/000555 and NDA 21-232) and is not part of this procedure. Nevertheless, the Applicant presented an overview of safety data for Orfadin capsules, including post-marketing data. The Applicant illustrates that Orfadin is well tolerated in HT-1 patients. The most frequently reported AEs in the studies are related to visual disorder (21 cases), including eye pain, keratitis, conjunctivitis, corneal opacity and photophobia; the eye symptoms were all transient and non-serious. In total 49 SAEs were reported, including acute liver failure (14 cases), hepatocellular carcinoma (10 verified, 6 not verified cases), multiorgan failure (1 case), transient

thrombocytopenia (3 cases), and elective liver transplantation (7 cases). The 3 cases of thrombocytopenia were the only SAEs considered related to Orfadin, whereas the other events are well known manifestations of HT-1. For 7 patients there were reports of leucopenia, which were regarded as non-serious AEs possibly related to Orfadin.

The postmarketing data show that the exposure up to 20 February 2013 (latest PSUR) is estimated to be 8016 patient years. A post marketing surveillance program was set at the time of the approval (Orfadin Active Surveillance, OAS) with the aim to stimulate reporting of AEs and to capture additional safety data in HT-1 patients particularly focusing on liver, renal, hematological, neurologic and ophthalmic function. The Applicant declares that OAS program provided data in line with the current knowledge of the safety profile of Orfadin.

The current MAA is for Orfadin oral suspension (nitisinone 4 mg/mL). The applicant reported safety data from the 2 clinical studies with Orfadin suspension on which the submission is based: the bioequivalence study in healthy volunteers (Sobi.NTBC-001) and the taste and palatability study in HT-1 pediatric patients (Sobi.NTBC-002).

Patient exposure

Study Sobi.NTBC-001: The study was performed in 12 male healthy volunteers. The subjects received 30 mg Orfadin 3 times over a period of 4 weeks. Each subject received capsules on one occasion and the suspension on two occasions (fasting and fed). In total, each subject received 90 mg Orfadin, whereof 60 mg as the suspension. The subjects, considered acceptable with regards to demographic characteristics, were male, 18 to 55 of age (mean age of 35 years) with a body mass index (BMI) of 18.5 to 30.0 kg/m2 (inclusive). The inclusion and exclusion criteria were acceptable. No subjects was withdrawn from the study. None of the deviations described above was judged to affect the study results or subject safety.

Study Sobi.NTBC-002: The study was performed in 18 paediatric patients with HT-1 and already under treatment with Orfadin capsules and diet restrictions. Twice daily administration of Orfadin suspension replaced the regular administration of Orfadin capsules during the 3-day study treatment period. For data presentation purposes, the patients were divided into 2 age groups: patients aged <5 years (n=6) and patients aged 5 to <18 years (n=12).The mean total daily dose of Orfadin suspension was 0.86 mg/kg which was the same as the mean dose prescribed for the capsule. The subjects ages ranged from 0.7 to 15.7 years (mean of 8.03 years).

Adverse events

Two different populations were included into the 2 studies presented for this submission; thus, no analysis of pooled safety data across the studies is performed. This is considered agreeable.

Sobi.NTBC-001

There were no deaths, other SAEs, or other significant TEAEs reported during study NTBC-001 and none of the AEs resulted in study drug discontinuation.

Both nitisinone formulations were considered safe and tolerable. The number of subjects reporting AEs did not differ between the suspension and capsule formulation.

All TEAEs were assessed as being mild in intensity, only one of the 8 TEAEs (episode of mild dizziness) was considered possibly related to study medication (administration of the suspension under fed conditions).

The administration of 30 mg nitisinone as a suspension or capsule was found to be safe and well tolerated by the study population.

Sobi.NTBC-002

No deaths, no SAEs, no discontinuations due to AEs or other significant AEs were reported in the study.

A total of 5 AEs were reported by 4 subjects, 2 aged < 5 years and 2 aged 5 to < 18 years. These AE were assessed as mild in intensity, 4 out of 5, 1 as moderate, none as severe. Only one AE was assessed as related to treatment drug. All AEs were unique events.

All but one AE (regurgitation) were assessed as not related to treatment and all were of mild intensity except for one (mouth hemorrhage), which was of moderate intensity. All AEs resolved without sequelae.

The Applicant concluded that in this study the 3 days treatment with the Orfadin suspension was safe and well tolerated by pediatric HT-1 patients

Serious adverse event / deaths / other significant events

There were no SAEs nor deaths in both the studies Sobi.NTBC-001 and Sobi.NTBC-002.

Laboratory findings

There were no clinically relevant changes or trends in the clinical laboratory evaluations in studies Sobi.NTBC-001 and Sobi.NTBC-002.

Safety related to drug-drug interactions and other interactions

No formal interaction studies with other medicinal products were conducted. In vitro data suggest some involvement of CYP3A4 in metabolism of nitisinone, and dose-adjustment may therefore be needed when nitisinone is co-administered with inhibitors or inducers of this enzyme.

In study Sobi.NTBC-001, food did not influence the bioavailability of nitisinone. When administered with food, nitisinone absorption from the suspension was slower than when administered under fasting conditions.

Discontinuation due to adverse events

No discontinuation due to administration of the drug in both the studies Sobi.NTBC-001 and Sobi.NTBC-002 were registered

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Safety information from the clinical studies with Orfadin capsules has been already evaluated in the initial application for the approval of Orfadin capsules and is not part of this procedure. In this application the Applicant reported safety data from the 2 clinical studies with Orfadin suspension: the bioequivalence study in healthy volunteers (Sobi.NTBC-001) and the taste and palatability study in HT-1 pediatric patients (Sobi.NTBC-002).

Overall, in these studies there were no deaths, other SAEs or discontinuation due to administration of the drug.

For study Sobi.NTBC-001, both formulations were considered safe and tolerable. All TEAEs were assessed as being mild in intensity, only one of the 8 TEAEs (episode of mild dizziness) was considered possibly related to study medication (administration of the suspension under fed conditions). The administration of 30 mg nitisinone as a suspension or capsule was found to be safe and well tolerated by the study population.

For study Sobi.NTBC-002, a total of 5 AEs were reported by 4 subjects, 2 aged < 5 years and 2 aged 5 to < 18 years. All AEs were unique events. Four out of 5 of these AEs were assessed as mild in intensity and 1 as moderate, none as severe. One child aged 8 months of age experience regurgitation (1 AE), that was considered by the investigator as related to treatment.

Considering that the Applicant demonstrated the bioequivalence of Orfadin suspension and Orfadin capsules, it is agreed to consider an adequate basis for a safety evaluation the established safety profile for the capsule formulation together with safety data collected for the oral suspension.

As concerns the safety of the excipients used, benzoic acid and its salts are known to displace the bilirubin from albumin (please refer to EMA/CHMP/508189/2013 and relevant warning proposed). A more cautious warning was considered necessary to be included into the SmPC section 4.4 compared to that reported by the EU guidance, in order to consider the conditions of the target population, and thus advising on the use of the capsules in patients at risk. The final agreed warning, taking into consideration the opinion of the PDCO Formulation Working Group, is the following:

Increase in bilirubin following its displacement from albumin, caused by benzoic acid and its salts, may increase jaundice in pre-term and full-term jaundiced neonates and develop into kernicterus (unconjugated bilirubin deposits in the brain tissue). A close monitoring of the plasma levels of bilirubin in the newborn patient is therefore of great importance. Bilirubin levels should be measured before start of treatment: in case of markedly elevated plasma levels of bilirubin, especially in premature patients with risk factors as acidosis and low albumin level, treatment with an appropriately weighed portion of an Orfadin capsule should be considered instead of the oral suspension until the unconjugated bilirubin plasma levels are normalised.

2.6.2. Conclusions on the clinical safety

There were no new, serious or unexpected safety findings when Orfadin suspension was administered either in healthy volunteers or in HT-1 paediatric patients in comparison to what has been previously reported for Orfadin capsules already approved.

A more cautious warning related to the presence of benzoate in the formulation was included into the SmPC section 4.4 compared to that reported by the EU guidance, in order to consider the conditions of the target population, and thus advising on the use of the capsules in patients at risk.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

A Pharmacovigilance Master File will be submitted at a later stage, before the implementation deadline of 2 July 2015.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Increased tyrosine levels
	Hypertyrosinemia related eye disorders
	Leukopenia/Granulocytopenia
Important potential risks	Lack of efficacy
	Developmental and cognitive disorders
	Embryo-fetal toxicity
	Exposure to nitisinone during breast-feeding
Important missing information	Interactions with substances known to induce or inhibit CYP3A4
	Carcinogenic potential
	Use in elderly
	Use in pregnant women
	Once daily administration

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Study Sobi.NTBC-005: Non-interventional voluntary PASS A non-interventional Post Authorization Safety Study (PASS) to evaluate long-term safety of Orfadin treatment in hypertyrosinemia type 1 (HT-1) patients in standard clinical care. Category 3.	Investigate Long Term Safety	Increased tyrosine levels, Hyper-tyrosinemia related eye disorders, Lack of efficacy, Development of liver cancer, Development of other malignancies, Developmental and cognitive disorders, Use in pregnant or breast feeding women	Ongoing (continuation of on-going Orfadin Active Surveillance)	Interim reports in PSUR planned 2015, 2016, 2017 Final study report April 2018
Study Sobi.NTBC-003: An open-label, non-randomized, sequential, multicenter study to evaluate the pharmacokinetics, efficacy and safety of once daily dosing compared to twice daily dosing of Orfadin in patients diagnosed with hereditary tyrosinemia type 1	Study to evaluate the appropiateness of once daily administration of Orfadin	Once daily dosing of Orfadin	Ongoing	Final study report December 2015

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Increased tyrosine levels	Text in SmPC: Warning in section 4.4 to monitor plasma tyrosine levels. Listed in section 4.8	None identified
Hypertyrosinemia related eye disorders	Text in SmPC: Warning in section 4.4 to perform slit lamp examination prior to treatment start, and examination of ophthalmologist on display of visual events. Listed in section 4.8	None identified
Leukopenia/Granulocytopenia	Text in SmPC: Warning in section 4.4 to monitor white blood cell counts regularly. Listed in section 4.8	None identified
Lack of efficacy	Text in SmPC: Warning in section 4.4 to monitor liver function regularly by liver function tests and imaging.	None identified
Developmental and cognitive disorders	No risk minimization measures identified.	None identified
Embryo-fetal toxicity	Text in SmPC: Pregnancy recommendation in section 4.6 to not use nitisinone during pregnancy unless clearly necessary.	None identified
Exposure to nitisinone during breast-feeding	Text in SmPC: Contraindication in section 4.3 to breast-feed. Section 4.6 states mothers receiving nitisinone must not breast-feed.	None identified

Interactions with substances known to induce or inhibit CYP3A4	Text in SmPC, section 4.5: No formal interaction studies with other medicinal products have been conducted. Nitisinone is metabolised in vitro by CYP 3A4 and dose-adjustment may therefore be needed when nitisinone is co-administered with inhibitors or inducers of this enzyme. Based on in vitro studies, nitisinone is not expected to inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4-mediated metabolism.	None identified
Carcinogenic potential	No risk minimization measures identified.	None identified
Use in elderly	No risk minimization measures identified.	None identified
Use in pregnant women	Text in SmPC: Pregnancy recommendation in section 4.6 to not use nitisinone during pregnancy unless clearly necessary.	None identified
Once daily administration	No risk minimization measures identified.	None identified

2.9. Product information

The Product Information has been revised as per current version of QRD template (QRD version 9, 03/2013) and includes the Orfadin 4 mg/ml oral suspension.

The proposed changes to product information are agreed.

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

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 the approved Orfadin capsules. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Orfadin (nitisinone), formulated as hard gelatin capsules, is approved for treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restrictions of tyrosine. The proposed new formulation, oral suspension, is considered valuable for the paediatric population as it facilitates dosage, could be useful in patients with difficulties in swallowing and is assumed to improve compliance, in view of the observation that the Orfadin suspension showed positive, or at least neutral scores, for taste and palatability in the dedicated study. The bioequivalence of Orfadin oral suspension to the capsule formulation is considered soundly demonstrated.

Uncertainty in the knowledge about the beneficial effects.

None

Risks

Unfavourable effects
Orfadin suspension was safe and well tolerated in the two studies submitted in this MAA: the bioequivalence study in healthy volunteers and the taste and palatability study in paediatric T-1 patients.

No deaths, other SAEs or discontinuation due to administration of the drug were reported.

No new or unexpected safety findings in comparison to what has been previously reported for Orfadin capsules have been reported. Considering that the bioequivalence of Orfadin suspension and Orfadin capsules has been demonstrated, it is agreed to consider an adequate basis for a safety evaluation the established safety profile for the capsule formulation together with safety data collected for the oral suspension.

Uncertainty in the knowledge about the unfavourable effects

None

Benefit-risk balance

Importance of favourable and unfavourable effects
The benefit represented by the availability of an age suitable formulation is considered to outweigh the risk represented by the small safety database of the oral suspension formulation in the paediatric population. Being the bioequivalence demonstrated between the capsule and the oral suspension the safety profile of the two formulations is assumed to be the same.

Benefit-risk balance
The benefit-risk balance of the oral suspension is considered positive.

Discussion on the benefit-risk balance

The overall risk benefit balance of Orfadin is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus/ that the risk-benefit balance of Orfadin in the 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 is favourable and therefore recommends the granting of the extension 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).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0276/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.