



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 June 2017
EMA/CHMP/502860/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nitisinone MendeliKABS

International non-proprietary name: nitisinone

Procedure No. EMEA/H/C/004281/0000

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	Adverse event
AFP	Alfa-fetoprotein
IEC	Independent ethics committee
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract research organization
eCRF	electronic Case Report Form
FAH	Fumarylacetoacetate hydrolase
HT-1	Hereditary tyrosinemia type 1
ICF	Informed consent form
MAH	Market authorization holder
PMS	Post-marketing surveillance program
p-Phe	Plasma phenylalanine
PSUR	Periodic Safety Update Report
p-Tyr	Plasma tyrosine
SA	Succinylacetone
SAE	Serious adverse event

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MendeliKABS Europe Ltd submitted on 4 March 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Nitisinone MendeliKABS, 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 23 July 2015.

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).

The applicant applied for the following indication: “Treatment of patients with confirmed diagnosis of hepatorenal 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 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
- Marketing authorisation holder: Swedish Orphan Biovitrum International AB
- Date of authorisation: 21/02/2005
- Marketing authorisation granted by:
 - Community
- Community Marketing authorisation number: EU/1/04/303/001-003

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

- Product name, strength, pharmaceutical form: Orfadin
- Marketing authorisation holder: Swedish Orphan Biovitrum International AB
- Date of authorisation: 21/02/2005
- Marketing authorisation granted by:
 - Community
- Community Marketing authorisation number: EU/1/04/303/001-003

- During the PRAC meeting on 9 March 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 March 2017, 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 22 May 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 June 2017.
- During the meeting on 22 June 2017, 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 Nitisinone MendeliKABS.

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation for Nitisinone MendeliKABS 2mg, 5mg and 10 mg hard capsules is submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended. The reference product is Orfadin 2, 5, and 10 mg 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).

Nitisinone (2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, or NTBC) is an inhibitor of the 4-hydroxyphenyl-pyruvate dioxygenase (HDDP), an enzyme involved in tyrosine degradation.

Nitisinone MendeliKABS 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.

Nitisinone MendeliKABS hard capsules are administered orally.

The recommended initial dose in the paediatric and adult population is 1 mg/kg body weight/day divided in 2 doses administered orally. 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.

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

Nitisinone MendeliKABS is presented as hard capsules containing 2 mg, 5 mg, or 10 mg of nitisinone as the active substance.

The other ingredient of the hard capsules content is pregelatinised maize starch. The capsule shell is composed of gelatin and titanium dioxide (E171); the printing ink comprises black iron oxide (E172) and shellac.

The product is available in HDPE plastic bottle with tamper-evident LDPE plastic cap, 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-(trifluoromethyl)benzoyl]-1,3-cyclohexanedione corresponding to the molecular formula $C_{14}H_{10}F_3NO_5$. It has a relative molecular mass of 329.23 g/mol and the following structure:

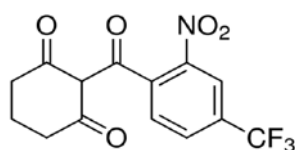


Figure 1. Structure of nitisinone.

The structure of the active substance (AS) has been sufficiently elucidated by a combination of IR, UV, ¹H-NMR, ¹³C-NMR, mass spectroscopy (MS), thermogravimetry (TGA), differential scanning calorimetry (DSC), and X-ray diffractometry (XRD).

Nitisinone appears as off-white to yellowish non-hygroscopic fine crystalline powder. It is practically insoluble in unbuffered water. It is freely soluble in dichloromethane, sparingly soluble in ethyl alcohol, slightly soluble in isopropyl alcohol and 70% aqueous isopropyl alcohol and in pH 6.8 phosphate buffer, very slightly soluble in pH 4.5 acetate buffer and practically insoluble at pH 1.1. Solubility in acidified aqueous media depends on the acid counter ion. Solubility increases with increasing pH. Its pKa was found to be around 10. Nitisinone is achiral and does not show polymorphism.

Manufacture, characterisation and process controls

Nitisinone is synthesized in three reaction steps followed by purification and packing. Each of the three reactions is monitored by HPLC for compliance to an in-process specification.

The starting materials are in line with the ICH Q11 requirements, are well-defined, commercially available and are controlled by acceptable specifications. As part of the AS manufacturing process one of the starting materials is recrystallised and controlled by suitable specification. The recrystallization step has been validated to ensure the starting material meets the relevant specification

The manufacturing process is controlled by appropriate in process controls and intermediate specifications where applicable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities including genotoxic impurities were well discussed with regards to their origin and characterised. It has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance.

Nitisinone is packaged in depyrogenated type I borosilicate glass bottle sealed with a GL-45 Polypropylene screw-cap. The materials comply with the relevant European requirements.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), identification (FTIR, $^1\text{H-NMR}$, $^{13}\text{C-NM}$, HPLC), assay (HPLC), impurities and degradation products (HPLC), elemental impurities (Ph. Eur.), residue on ignition (Ph. Eur.), water content (Ph. Eur.), residual solvents/catalysts/counterions, (GC-FID, HPLC, Chemical Reaction, FAA), X-Ray diffraction (XRD) and microbial quality (Ph. Eur.). In addition, the specification includes tests and limits for relevant catalysts and reagents.

Based on the data provided, the fate and carry-over of impurities has been sufficiently demonstrated. The potential impurities and possible genotoxic impurities which are possible from the defined starting materials are controlled in the final active substance by validated test methods and suitable limits for unknown potentially genotoxic impurities as per ICH M7.

The analytical methods used have been adequately described and non-compendial methods 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 from three production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three consecutive full scale nitisinone batches stored in the intended commercial packaging for up to 24 months under long term conditions ($-80\text{ }^\circ\text{C}$ and $-20\text{ }^\circ\text{C}$) were provided. Data for one batch under accelerated conditions ($25\pm 2\text{ }^\circ\text{C}$ / $60\pm 5\%$ RH) for 24 months, and for all three stability batches under accelerated conditions ($5\text{ }^\circ\text{C} \pm 3\text{ }^\circ\text{C}$) for up to 24 months according to the ICH guidelines were provided. Samples were tested for appearance, identification, assay, impurities, degradation products and water content. Samples under $25\pm 2\text{ }^\circ\text{C}$ / $60\pm 5\%$ RH were also tested for microbiological quality. The analytical methods used were the same as for release and were stability indicating. No degradation or degradation products higher than 0.05 % have been observed in these batches at any of the tested storage temperatures. No significant changes to any of the measured parameters were observed under either storage condition and all remained within specification (long term and accelerated conditions). Following the replacement of the bottle caps with another cap of exactly the same material the applicant committed to place the next three active substance batches into stability studies at the intended storage temperature ($-20 \pm 5\text{ }^\circ\text{C}$) using this new container-closure system and then, one batch per year for the following three years.

Stress testing on one commercial scale batch in aqueous solutions and in solid state was performed. Photostability as per ICH Q1B was also performed as part of this study. The primary aim of these studies was to validate the stability indicating character of the analytical method and to determine major degradation products. Samples were subjected to basic and acidic conditions, oxidation, and thermal and photo degradation (ICH Q1B). The degradation pathways and the stability indicating power of the assay and related substance methods have been demonstrated.

Given the nitrated nature of nitisinone, storing it at room temperature could result in the production of trace genotoxic impurities which are prohibited by ICH M7. The proposed storage condition was set as a precaution to limit the possible formation of trace impurities. The proposed storage condition is acceptable as it is of no concern to patients and therefore not a problem as such.

The stability results justify the proposed retest period of 24 months in the proposed container and storage condition.

2.2.3. Finished medicinal product

Pharmaceutical development

Description of the product and pharmaceutical development

The finished product is presented as an immediate release white hard gelatin capsule printed with black ink "2 mg" or "5 mg" or "10 mg" on the cap and "Nitisinone" on the body. Nitisinone MendeliKABS is available in three different strengths: 2 mg, 5 mg and 10 mg.

The aim of the pharmaceutical development work was to develop a generic product which would be bioequivalent to the reference product Orfadin 2, 5, and 10 mg hard capsules.

It was known from literature that partially pre-gelatinized maize starch was selected based on regulatory compliance, bulk/tapped density ranges and particles size distribution criteria. It was found to be an appropriate choice to obtain homogeneous dry blends with milled nitisinone. The composition of the finished product, dosage form and concentration are the same as of the reference product. No alternative formulations were investigated. All ingredients were formulated to match the reference product for each specific attribute. This approach is generally acceptable considering the simple nature of the formulation and finished product. Compatibility of the active substance and the proposed excipient was studied.

Nitisinone is BCS class I compound. In order to study the impact of milling on dissolution rates in acidic media, the dissolution profiles of the hand milled Nitisinone 10 mg prototype were compared with that of the unmilled Nitisinone 10 mg capsules at both pH 4.5 and pH 1.2. In acidic dissolution media capsules with milled nitisinone dissolved substantially faster than those containing unmilled nitisinone. Therefore particle size is controlled as an in process control after milling.

It has been further shown that the most discriminatory dissolution conditions have been selected as the QC method.

Bioequivalence versus the reference product has been demonstrated by an *in vivo* study comparing the highest applied strength 10 mg. Comparative dissolution profiles as required by the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) have been provided. Biowaivers were requested for the two lower strengths 5 mg and 2 mg. Dissolution profiles similarity factors (F_2) between the 5 mg and 2 mg strengths against the 10 mg biobatch were also calculated and found similar as per the recommendation in the above guideline. The F_2 values calculated were above 50 and thus the dissolution profiles could be considered similar. Therefore, the biowaiver for the 5 mg and 2 mg dosage strength is considered justified and acceptable.

Given the simplicity of the manufacturing process and small batch sizes required by the small number of patients, process development was performed on representative batches of capsules using standard powder processing conditions.

The primary packaging of Nitisinone MendeliKABS hard capsules was selected as 50 ml HDPE plastic container with a snap-on neck and LDPE plastic push-fit tamper-evident cap. The primary packaging material conforms to all relevant EU and Ph. Eur. guidelines.

Manufacture of the product

The manufacturing process can be considered as a standard process which comprises milling, V-blending and encapsulating.

The applicant used a QbD approach for risk assessment study during manufacturing process development. Critical Process Parameters (CPPs) and process validation protocol were based on a risk assessment study performed during process development. The critical quality attributes (CQAs) have been identified are assay impurities and degradation products, dissolution and uniformity of dosage unit. The blending procedure includes critical dynamic process parameters affecting CQAs and is controlled by in-process testing. Holding times and appropriate storage conditions have been established and justified.

Currently, as the size of the biobatch is extremely small and corresponds to the smaller part of the proposed commercial batch size range, to avoid potential problems with scale up, the batch size is limited to the size of the biobatch.

Validation of the manufacturing process was carried out using eight consecutive full scale batches of 2 mg, 5 mg, or 10 mg capsules prepared from three different lots of active substance. The validation results have demonstrated that the manufacturing process is robust and consistently yields a product capable of meeting the pre-defined quality characteristics.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (HPLC), assay (HPLC), impurities and degradation products (HPLC), dissolution (HPLC), uniformity of dosage units (Ph. Eur. - content uniformity) and microbiological test (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data on eight commercial scale batches were presented. All batches are representative of the commercial formula and manufacturing process. All batches met the commercial specification limits.

Stability of the product

Stability data from eight commercial scale batches covering all strengths stored under long term conditions (5 °C ±3 °C) for up to 12 months (and up to 18 months for a total of five batches covering all strengths), for up to 12 months at 25 °C ±2 °C/60% ±5% RH (and up to 18 months for a total of five batches covering all strengths) and for up to six months at 40 °C /75% RH and 30 °C /65% RH according to the ICH guidelines were provided. 25 °C /60% RH, 30 °C /65% RH and 40 °C /75% RH were considered accelerated conditions. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, identification, assay, dissolution, related substances and microbiological test. The methods used were the same (apart from dissolution which has been changed) as for release testing, are validated and stability indicating. There was no significant change in any of characteristics tested at any time point and no trends were observed. However, the thermal degradation product (cyclization product in specifications) was observed in all lots stored at 25 °C, 30 °C and 40 °C. Linear regression analyses of stability data showed that degradation of nitisinone to cyclization product is a linear function of time, both at 25 °C and 40 °C.

Stress testing under aqueous acidic and basic condition, heat, oxidation and light was performed on one commercial scale batch. Photostability as per ICH Q1B was also performed as part of this study. The 10 mg formulation was photostable in the solid state, whereas the 2 mg formulation was slowly

degraded by UV-visible light in the solid state. Accordingly, blends should be stored during in-process hold time in light tight containers and a storage precaution has been included in the SmPC (section 6.3).

Taking into account the package size (60 capsules) and the administration according to the SmPC and that the product is not moisture sensitive, the in-use stability is not considered relevant aspect for this product. However the applicant should perform an in-use stability study to confirm the stability of the product under the recommended use conditions.

Based on the provided stability data, the proposed shelf life of 18 months stored in the original package at 5 ± 3 °C and protected from light, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine for the capsules used in the product is obtained from porcine sources. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

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. 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.

2.2.6. Recommendation 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:

- An in-use stability study should be performed to confirm the stability of the product under the recommended use conditions.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

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

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Nitisinone MendeliKABS is considered unlikely to result in any significant increase in the combined sales volumes for all nitisinone containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Conclusion on the non-clinical aspects

No non-clinical studies were provided within current application. A non-clinical overview has been provided and was based on up-to-date and adequate scientific literature. 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 hard capsules containing nitisinone. To support the marketing authorisation application the applicant conducted one bioequivalence study with parallel design under fasting conditions. This study was the pivotal study for the assessment.

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

For the clinical assessment the *EMA Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98) as well as *the EMA Guideline on Bioanalytical method validation* (EMEA/CHMP/EWP/192217/09) in their current version, are of particular relevance.

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

To support this application the applicant has submitted one bioequivalence study conducted with the **10 mg capsule strength under fasting conditions**.

Study 150207: Randomized, blind, 1-way parallel bioequivalence study of Nitisinone 10 mg capsule and Orfadin (reference) following a 10 mg dose in healthy subjects under fasting conditions.

To fulfil the requirements of **a biowaiver for other strengths, 2 mg and 5 mg hard capsules**, dissolution testing was performed at three pH levels. The evidence submitted in response to Day 120 List of Questions showed that *in vitro* dissolution profiles are similar and the data presented is sufficient to grant a biowaiver for the proportional formulation of lower strengths since the necessary information has been provided. This was in line with *EMA Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98).

Clinical studies

To support the application, the applicant has submitted **one bioequivalence study (Study 150207)**.

2.4.2. Pharmacokinetics

Study 150207: Randomized, blind, 1-way parallel bioequivalence study of Nitisinone 10 mg capsule and Orfadin (reference) following a 10 mg dose in healthy subjects under fasting conditions.

Table 3: Tabular overview of clinical study

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of administration	Number of Subjects	Condition	Duration of Treatment	Study Status; Type of Report
BE	150207	Module 5.3.1.2	To compare the rate and extent of absorption of Test product versus Reference product; bridging results from literature to the test product.	Randomised, parallel, blinded, single-dose, 1-period	Test: Nitisinone-MDK capsule, 10 mg, oral, fasting condition Reference: Orfadin [®] capsule, 10 mg, oral, fasting condition	46 (23 in each group)	Healthy adult subjects	Single dose	Completed; Full report

Methods

Study design

This was a single centre, randomised, single-dose, blinded, 1-period, parallel bioequivalence study to compare the rate and extent of absorption of a Nitisinone-MDK versus Orfadin under fasting conditions. According to the randomisation scheme, subjects were administered a single oral dose of either the Test or Reference (Orfadin) study medication, as a 1 x 10 mg capsule.

CRO: inVentiv Health Clinique Inc., Quebec, Canada.

Sponsor: MendeliKABS Inc., Canada

Site and dates of clinical part of the study: inVentiv, Quebec, Canada; 30/06/2015 to 05/08/2015. First dose was administered on 20/07/2015.

Site and dates of analytical part of the study: inVentiv, Quebec, Canada; 03/08/2015 to 06/08/2015.

Biostatisticians and bio-statistical institute: inVentiv Health Clinique Inc., Quebec, Canada.

Test and reference products

Nitisinone MendeliKABS 10 mg capsule manufactured by KABS Laboratories, Canada (batch No F150417-001, manufacturing date: 07/04/2015, expiry/retest date: 01/2016) has been compared to

Orfadin 10mg hard gelatin capsule manufactured by Swedish Orphan Biovitrum International (SOBI) AB, Sweden; manufactured by Apotek Produktion and Laboratorier AB, Sweden; batch No.3038429 from Sweden market, expiry date: 30/09/2016.

Population studied

A total of 46 healthy adult subjects (aged 19 – 53 years, BMI 19.45 – 29.76, 25 male and 21 female subjects) were included in the study. 23 subjects were randomly assigned to each treatment groups in parallel designed study. Moderate smokers (no more than nine cigarettes or equivalent daily) or non-smokers were allowed in this study. 46 subjects completed both study phases and were included in the pharmacokinetic and statistical analysis. No major protocol deviations were reported. Inclusion and exclusion criteria were presented and were acceptable for a BE study and for the product under investigation. Drop outs: None.

Analytical methods

Plasma concentrations of Nitisinone were determined using a validated reversed phase LC-MS/MS methods. Study drugs were extracted from 50 µl of plasma by automated protein precipitation. Nitisinone-13C6 was used as internal standards.

8 non-zero calibrates and 4 levels of QC samples containing Nitisinone were used. Calibration standards ranged from 5 ng/ml to 5000.0 ng/ml, LOQ was 5.0 ng/ml. The quality control (QC) concentrations were 15.0 ng/ml, 375.0 ng/ml, 2500 ng/ml and 3750.0 ng/ml.

The concentrations were calculated using peak area ratios and the linearity of the calibration curve was determined using least squares regression analysis employing a weighted ($1/x^2$) linear ($y=mx+b$) for Nitisinone.

Pre-study validation and bio-analytical report are presented. The method selectivity and sensitivity were demonstrated. Stability of analytes at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation. Dilution integrity, carryover and matrix effect were tested. Composition of analytical runs has been described.

Incurred sample reanalysis was conducted on 101 samples (10% of 1009 samples). 100% (101/101) of concentrations obtained by reanalysis were found within 20% of their mean initial value.

Blood samples were collected into K₂EDTA tubes and centrifuged. The plasma samples were frozen and retained at -80°C until assay. The maximum study sample storage period from first blood draw (20/07/2015) to last sample analysis (06/08/2015) was 17 days for Nitisinone. The long-term stability of Nitisinone in human plasma covers 193 days at -80°C. All concentration values below limit of quantification were set as zero for PK analysis.

Reanalysis of study samples: A total of 1009 study samples were analysed in 6 analytical runs. Two (0.2%) samples were re-analysed due to the loss of sample during processing.

Pharmacokinetic variables

Primary variables: C_{max} and AUC_{0-72} .

Pharmacokinetic parameters C_{max} , T_{max} , AUC_{0-t} , AUC_{0-72} , $AUC_{0-\infty}$, residual area, K_{el} and $T_{1/2el}$ were determined.

Statistical methods

Pharmacokinetic and statistical analyses were performed using Pharsight® Knowledgebase Server™ (PKS) version 4.0.2 and Phoenix® WinNonlin® 6.4, which were validated for bioequivalence studies by inVentiv. These software perform non-compartmental analyses of pharmacokinetic parameters and statistical analyses (via SAS version 9.2). Figures were generated using R (version 3.0.1 or higher).

PK parameters for each individual were tabulated and graphically presented. AUC_{0-72} was calculated using the linear trapezoidal rule. ANOVA was performed on the ln-transformed C_{max} , AUC_{0-72} and $AUC_{0-\infty}$. Non-parametric analysis of T_{max} was performed on untransformed data. The statistical model included treatment as factor for the subsequent ANOVA analysis.

Criteria for conclusion of bioequivalence:

The ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-72} were all to be within the 80.00 to 125.00% bioequivalence range.

Results

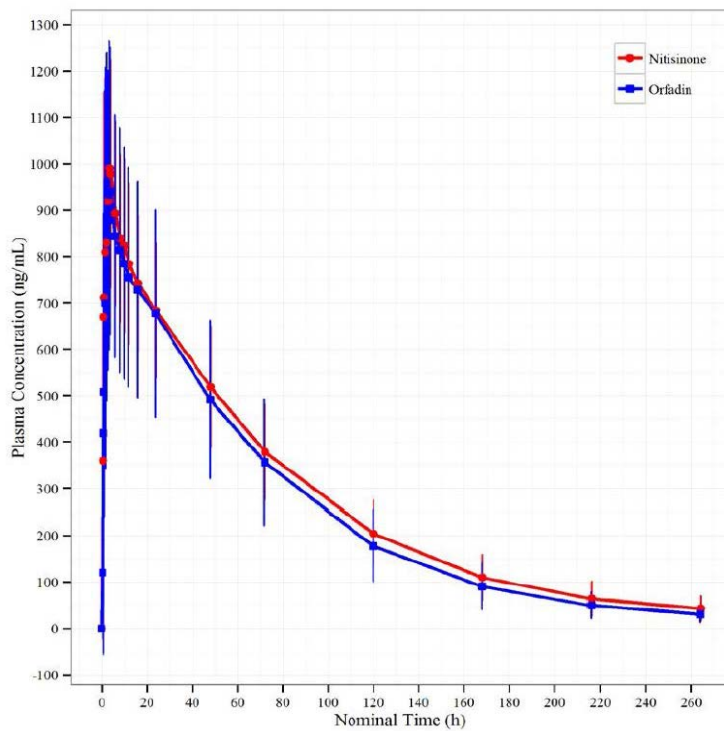
Table 1: Pharmacokinetic parameters for Nitisinone (non-transformed values)

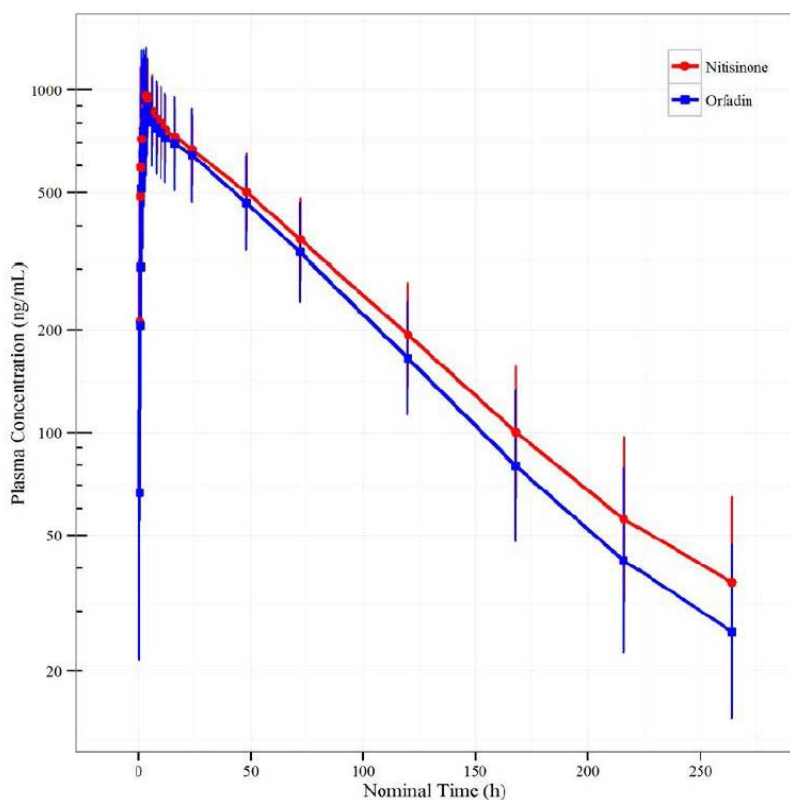
Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic	SD
$AUC_{(0-t)}$ (h*ng/mL)	71830.85	±18597.78	66573.91	± 24406.39
$AUC_{(0-\infty)}$ (h*ng/mL)	76244.45	±20904.50	69139.54	± 25813.08
$AUC_{(0-72)}$ (h*ng/mL)	43785.40	±9691.38	42004.83	±13876.04
C_{max}	1103.87	±272.52	1057.78	± 335.34
T_{max}^*	2.50 (0.750 – 4.00)		2.00 (0.750– 8.00)	
< AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>			
< AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours>			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 2: Statistical analysis for Nitisinone (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV*
AUC _(0-72h)	106.66%	93.02% - 122.30%	28.15%
C _{max}	105.62%	91.38% - 122.08%	29.86%
*The inter-subject CVs			

Linear and semi-logarithmic plots of mean plasma concentrations of Nitisinone after administration of Test and Reference formulations (10 mg capsules) to healthy subjects.





Safety data

No serious adverse event (AE) was recorded in this study. A total of 13 adverse events (AEs) were reported by 8 of the 46 subjects who received at least one dose of the study medication. The breakdown by treatment group is as follows: 6 AEs reported by 17.4% (n=4) of the 23 subjects who received Nitisinone MendeliKABS and 7 AEs reported by 17.4% (n=4) of the 23 subjects who received Orfadin. The most commonly reported AE was "headache" reported by 6.5% (n=3) of subjects. All 13 AEs reported during the study were graded as mild in severity. Of the 13 AEs reported, the relationship to the treatment of 8 was judged as possible and 5 as unrelated.

Conclusions

Based on the presented bioequivalence study Nitisinone MendeliKABS was considered bioequivalent with Orfadin.

2.4.3. Discussion on clinical aspects

The current application concerns an oral immediate release formulation. Because the $T_{1/2}$ of nitisinone in plasma ranges from 39 to 86 hours, a 1-period parallel design was chosen by Applicant for this study. Considering pharmacokinetics of the drug under investigation, this approach was considered acceptable.

According to the SmPC of the reference product, no specific recommendation regarding food intake is given except that if nitisinone treatment with Orfadin hard capsules is initiated with food, this should be maintained on a routine basis. This recommendation is derived from empirical results as nitisinone

has been co-administered with food during the generation of efficacy and safety data for originator product. No formal food interactions studies have been performed with Orfadin capsules. Therefore, the conduct of the single dose study under fasting condition as most sensitive condition to detect a potential difference between formulations was considered adequate.

Nitisinone pharmacokinetics is dose proportional, therefore the conduct of the BE study at highest strength (10 mg) was considered sufficient. Study design was acceptable in general terms and in line with pharmacokinetic properties of nitisinone. The study was conducted under standardised conditions. The sampling period was adequate and was more than 72 hr. The AUC_{0-t} was calculated up to 264 hrs. T_{max} was not observed in any subject in the first sample time point. The Residual area was lower than 20% for all subjects indicating that the duration of sampling was sufficient for nitisinone.

Data regarding test product were sufficient. The bio-batch size is considered sufficient. The Certificates of Analysis of the Reference and Test products were included in the dossier. The reference product is acceptable as it is a known product authorised within EU community.

The population was chosen according to the guidelines, the sample size was found adequate.

Pre- and within study validation for the determination of nitisinone in human plasma was considered sufficient. Long term stability data was presented for 7 days at -20°C and -80°C in validation report. The extended long-term stability data were also provided. The long-term stability of Nitisinone in human plasma is now demonstrated for 193 days at -80°C.

The handling of samples was sufficiently described; the SOPs were provided. Results of ISR analysis were presented.

The pharmacokinetic parameters calculated are appropriate for a single dose study.

Standard bioequivalence criteria are proposed for C_{max} and AUC₀₋₇₂.

The 90% confidence intervals for ln-transformed pharmacokinetic variables C_{max} and AUC₀₋₇₂ were within the conventional bioequivalence range of 80% to 125%. ANOVA did not detect any statistically significant (p -values > 0.05) differences between treatments for AUC_{0-t}, AUC₀₋₇₂, AUC_{0-inf}, and C_{max}.

Any subjects did not reach C_{max} at the first sampling time point indicating that sampling time schedule was adequate. The duration of sampling was sufficient. The %AUC_{extrap} values were not applicable because sampling scheme reached out to 264 hours. The Residual area was less than 20% for all subjects.

The pharmacokinetic variables for nitisinone were comparable between test and reference product. Both formulations were equally tolerated in the study.

Based on the presented bioequivalence study, nitisinone 10 mg capsule by KABS Laboratories, Canada was considered bioequivalent with Orfadin 10 mg hard gelatine capsule by Swedish Orphan Biovitrum International (SOBI) AB, Sweden.

2.4.4. Conclusions on clinical aspects

To support the application, the applicant has submitted one bioequivalence study. It was a randomized, blind, 1-way parallel bioequivalence study of nitisinone 10 mg capsule and Orfadin (reference) following a 10 mg dose in healthy subjects under fasting conditions. The concerns raised during the procedure regarding the BE have been satisfactorily answered and the product is

approvable from the clinical point of view. No additional clinical studies were provided within current application. A clinical overview has been provided and was based on up-to-date and adequate scientific literature. The CHMP considered this application acceptable from clinical point of view.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> - Increased tyrosine levels - Hypertyrosinemia related eye disorders - Leukopenia / Granulocytopenia
Important potential risks	<ul style="list-style-type: none"> - Lack of efficacy - Developmental and cognitive disorders - Embryo-fetal toxicity - Exposure to nitisinone during breast-feeding
Missing information	<ul style="list-style-type: none"> - 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)
Pan-Canadian Patient Registry (similar to category 3)	To evaluate the long-term safety of Nitisinone MendeliKABS	Increased tyrosine levels Hypertyrosinemia related eye disorders Leukopenia / Granulocytopenia Lack of efficacy Developmental and cognitive disorders Embryo-fetal toxicity Exposure to nitisinone during breast-feeding Interactions with substances known to induce or inhibit CYP3A4 Carcinogenic potential Use in elderly Use in pregnant women Off-label use	Planned start date: Q3 2017	To be determined

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Increased tyrosine levels	<p>Text in SmPC (section 4.2 Posology and method of administration):</p> <p><i>Adjunct to the nitisinone treatment, a diet deficient in phenylalanine and tyrosine is required and should be followed by monitoring of plasma amino acids.</i></p> <p>Text in SmPC (section 4.4 Special warnings and precautions for use):</p> <p><i>Monitoring of plasma tyrosine levels</i> <i>It is recommended that a slit-lamp examination of the eyes is performed before initiation of nitisinone treatment. A patient displaying visual disorders during treatment with nitisinone should without delay be examined by an ophthalmologist. It should be established that the patient is adhering to his dietary regimen and the plasma tyrosine concentration should be measured. A more restricted tyrosine and phenylalanine diet should be implemented in case the plasma tyrosine level is above 500 µmol/L. It is not recommended to lower the plasma tyrosine concentration by reduction or discontinuation of nitisinone, since the metabolic defect may result in deterioration of the patient's clinical condition.</i></p> <p>Text in SmPC (section 4.8 Undesirable effects):</p> <p><i>Nitisinone treatment is associated with elevated tyrosine levels. Elevated levels of tyrosine have been associated with corneal opacities and hyperkeratotic lesions. Restriction of tyrosine and phenylalanine in the diet should limit the toxicity associated with this type of tyrosinemia.</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	None proposed.
Hypertyrosinemia related eye disorders	<p>Text in SmPC (section 4.2 Posology and method of administration):</p> <p><i>Adjunct to the nitisinone treatment, a diet deficient in phenylalanine and tyrosine is required and should be followed by monitoring of plasma amino acids.</i></p> <p>Text in SmPC (section 4.4 Special warnings and precautions for use):</p> <p><i>Monitoring of plasma tyrosine levels</i> <i>It is recommended that a slit-lamp examination of the eyes is performed before initiation of nitisinone treatment. A patient displaying visual disorders during treatment with nitisinone should without delay be examined by an ophthalmologist. It should be established that the patient is adhering to his dietary regimen and the plasma tyrosine concentration should be measured. A more restricted tyrosine and phenylalanine diet should be implemented in case the plasma tyrosine level is above 500 µmol/L. It is not</i></p>	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p><i>recommended to lower the plasma tyrosine concentration by reduction or discontinuation of nitisinone, since the metabolic defect may result in deterioration of the patient's clinical condition. [...]</i></p> <p><i>Monitoring visits should be performed every 6 months; shorter intervals between visits are recommended in case of adverse events.</i></p> <p>Text in SmPC (section 4.8 Undesirable effects): <i>Nitisinone treatment is associated with elevated tyrosine levels. Elevated levels of tyrosine have been associated with corneal opacities and hyperkeratotic lesions. Restriction of tyrosine and phenylalanine in the diet should limit the toxicity associated with this type of tyrosinemia.</i></p> <p>Listed in SmPC (section 4.8 Undesirable effects): <i>Eye disorders</i> <i>Common: conjunctivitis, corneal opacity, keratitis, photophobia, eye pain</i> <i>Uncommon: blepharitis</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	
Leukopenia / Granulocytopenia	<p>Text in SmPC (section 4.4 Special warnings and precautions for use): <i>Platelet and white blood cell (WBC) monitoring</i> <i>It is recommended that platelet and white cell counts are monitored regularly, as a few cases of reversible thrombocytopenia and leucopenia were observed during clinical evaluation.</i></p> <p><i>Monitoring visits should be performed every 6 months; shorter intervals between visits are recommended in case of adverse events.</i></p> <p>Listed in SmPC (section 4.8 Undesirable effects): <i>Blood and lymphatic system disorders</i> <i>Common: leucopenia, granulocytopenia</i> <i>Uncommon: leukocytosis</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	None proposed.
Important Potential Risks		
Lack of efficacy	<p>Text in SmPC (section 4.2 Posology and method of administration): <i>Dose adjustment</i> <i>During regular monitoring, it is appropriate to follow urine succinylacetone, liver function test values and alpha-fetoprotein levels (see section 4.4). If urine succinylacetone is still detectable one month after the start of nitisinone treatment, the nitisinone dose should be increased to 1.5 mg/kg body weight/day divided in 2 doses. A dose of 2 mg/kg body weight/day may be needed based on the evaluation</i></p>	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p><i>of all biochemical parameters. This dose should be considered as a maximal dose for all patients.</i></p> <p><i>If the biochemical response is satisfactory, the dose should be adjusted only according to body weight gain.</i></p> <p><i>However, in addition to the tests above, during the initiation of therapy or if there is a deterioration, it may be necessary to follow more closely all available biochemical parameters (i.e. plasma succinylacetone, urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity).</i></p> <p>Text in SmPC (section 4.4 Special warnings and precautions for use): <i>Liver monitoring</i> <i>The liver function should be monitored regularly by liver function tests and liver imaging. It is recommended also to monitor serum alpha-fetoprotein concentration. Increase in serum alpha-fetoprotein concentration may be a sign of inadequate treatment</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	
Developmental and cognitive disorders	<p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	None proposed.
Embryo-fetal toxicity	<p>Text in SmPC (section 4.6 Fertility, pregnancy and lactation): <i>Pregnancy</i> <i>There are no adequate data from the use of nitisinone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Nitisinone should not be used during pregnancy unless clearly necessary.</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p> <p>Questionnaire for follow-up of drug exposure during pregnancy.</p>	None proposed.
Exposure to nitisinone during breast-feeding	<p>Text in SmPC (section 4.3 Contraindications): <i>Mothers receiving nitisinone must not breast-feed.</i></p> <p>Text in SmPC (section 4.6 Fertility, pregnancy and lactation): <i>Lactation</i> <i>It is not known whether nitisinone is excreted in human breast milk. Animal studies have shown adverse postnatal effects via exposure of nitisinone in milk. Therefore, mothers receiving nitisinone must not breast-feed, since a risk to the suckling child</i></p>	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p><i>cannot be excluded.</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	
Important Missing Information		
Interaction with substances known to induce or inhibit CYP3A4	<p>Text in SmPC (section 4.5 Interaction with other medicinal products and other forms of interaction):</p> <p><i>No formal interaction studies with other medicinal products have been conducted.</i></p> <p><i>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.</i></p> <p><i>Based on in vitro studies, nitisinone is not expected to inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4-mediated metabolism.</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	None proposed.
Carcinogenic potential	<p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	None proposed.
Use in elderly	<p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	None proposed.
Use in pregnant women	<p>Text in SmPC (section 4.6 Fertility, pregnancy and lactation):</p> <p><i>Pregnancy</i></p> <p><i>There are no adequate data from the use of nitisinone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Nitisinone should not be used during pregnancy unless clearly necessary.</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p> <p>Questionnaire for follow-up of drug exposure during pregnancy.</p>	None proposed.
Once daily administration	<p>Text in SmPC (section 4.2 Posology and method of administration):</p> <p><i>The recommended initial dose in the paediatric and adult population is 1 mg/kg body weight/day divided in 2 doses administered orally.</i></p> <p>Prescription only medicine.</p> <p>Supervision by physicians experienced in the treatment of hereditary metabolic disorders.</p>	None proposed.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of nitisinone hard capsules. The reference product Orfadin® 10 mg hard gelatine capsule name 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.* 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 single centre, randomised, single-dose, blinded, 1-period, parallel design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements.

The application concerns an oral immediate release formulation. Because the T_{1/2} of Nitisinone in plasma ranges from 39 to 86 hours, a 1-period parallel design was chosen by Applicant for this study. Considering pharmacokinetics of the drug under investigation, this approach is considered acceptable.

No specific recommendation regarding food intake is given in the product information of the reference product except that if nitisinone treatment is initiated with food, this should be maintained on a routine basis. It was considered that the conduct of the single dose study under fasting condition as

most sensitive condition to detect a potential difference between formulations is considered adequate. Nitisinone pharmacokinetics is dose proportional, therefore the conduct of the BE study at highest strength (10 mg) was considered sufficient. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Nitisinone MendeliKABS met the protocol-defined criteria for bioequivalence when compared with the Orfadin. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} 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.

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 Nitisinone MendeliKABS is favourable in 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 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.

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

Not applicable.