22 April 2022
EMA/255082/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Insulatard

International non-proprietary name: insulin human

Procedure No. EMEA/H/W/005780/0000

Note

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 24 June 2021 an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organisation for Insulatard®.

The eligibility by the World Health Organisation was agreed-upon on 12 November 2020.

Insulatard® will exclusively be intended for markets outside the European Union.

The applicant applied for the following indication: Treatment of diabetes mellitus

1.2. Legal basis, dossier content

The legal basis for this application refers to:

This application is submitted under Article 58 of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to Article 8(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.4. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: N/A

The application was received by the EMA on	24 June 2021
The procedure started on	15 July 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 October 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	15 October 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 November 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 December 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs'	1 February 2022

Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' Joint Updated Assessment Report to all CHMP and PRAC members on	17 February 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	24 February 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	6 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' Joint Updated Assessment Report to all CHMP and PRAC members on	13 April 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Insulatard® on	22 April 2022

2. Scientific discussion

2.1. Problem statement

This is an application for Insulatard® (insulin human) submitted under article 58 of regulation (EC) No 726/2004 (H0005779). Eligibility for submission of this application under Article 58 was confirmed by EMA and WHO on 12 November 2020. The therapeutic indication for Insulatard® is 'treatment of diabetes mellitus'. Insulatard® is currently approved in the EU with product number EMEA/H/C/000441. Insulatard® is approved and has been marketed globally for more than 30 years. At present, Insulatard® is approved in 151 countries and launched in 141 countries. The product is also available in countries that do not require a registration or which are supported by registration in another country (e.g. provided via distributors or special deliveries).

The purpose of this application is to get an assessment of a proposed update to the storage conditions for Insulatard® in order to further facilitate the use of the product in relevant countries with challenging temperature conditions and limited access to refrigeration. It is important to emphasize that the product included in the present application is identical to the currently approved product in the EU, apart from the proposed update to the storage conditions.

The background for this application is that Novo Nordisk has received requests from international humanitarian, public health and academic organisations to address challenges with insulin thermostability.

2.1.1. Disease or condition

Diabetes mellitus (DM) is the most common endocrine disease characterised by hyperglycaemia in the pre- and postprandial state resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus is classified into a primary form without any associated disease being present, while in the secondary variety; some identifiable condition, causes or allows a diabetic syndrome to develop. These involve pancreatic diseases, hormonal causes, defects in insulin receptors, genetic syndromes. The prevalence of diabetes mellitus is approximately 3%.

Acute, life-threatening consequences of diabetes are hypoglycaemia, and hyperglycaemia with ketoacidosis or non-ketotic hyperosmolar syndrome. Long-term complications of diabetes include microvascular disorders such as: retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy causing foot-ulcers and autonomic neuropathy leading to gastrointestinal, genitourinary, and sexual dysfunction. The long-term complications also include macrovascular disease with an increased incidence of atherosclerotic cardiovascular, peripheral, and cerebrovascular disease.

Insulin is a key hormone in human metabolism. It lowers blood glucose by suppressing hepatic glucose production by inhibiting gluconeogenesis and stimulating liver glycogen synthase, and by stimulating peripheral glucose uptake in fat and muscle tissue. Furthermore, insulin stimulates lipogenesis by increasing glucose uptake into adipocytes and it inhibits breakdown of triglycerides. Additionally, insulin promotes formation and prevents degradation of proteins by stimulating active transport of amino acids into cells. Insulin exerts its many biological effects by binding to a specific cell-surface receptor on its target tissues.

Type 1 DM is characterised by loss of insulin production due to destruction of pancreatic beta cells as a result of an auto immune response or idiopathic causes. Genetic and environmental factors seem to be involved in the off-set of the autoimmune process in a not yet fully explored manner.

The rate of beta-cell mass destruction is variable, being rapid in some persons (mainly infants and children) and slow in others (mainly adults), and eventually leads to absolute insulin deficiency. When 90% of the beta-cell mass is lost due to these mechanisms the disease becomes overt often in an acute manner with ketoacidosis and dehydration. Once symptoms develop, insulin therapy is required. Occasionally, an initial episode of ketoacidosis is followed by a symptom free interval (the "honeymoon" period), during which no or reduced treatment is required. However, all Type 1 diabetic patients will need exogenous insulin to survive.

Type 2 DM is characterised by increased peripheral insulin resistance, impaired and abnormal insulin secretion with loss of first phase insulin secretion and increased hepatic glucose output. These patients are often furthermore affected by obesity, hypertension and lipid disorders. Symptoms begin gradually, and the diagnosis is frequently made when an asymptomatic person is found to have an elevated plasma glucose level on routine laboratory examination. Type 2 DM patients only seldom develop ketoacidosis. Treatment of these patients starts most often with diet. When failing on diet, treatment with beta-cell secretagoques or insulin sensitizers has to he initiated. When the beta-cell function eventually becomes even more impaired, patients do end up in a situation where only exogenous insulin can restore metabolic control.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Type 1 DM, which usually is diagnosed in childhood or adolescence, accounts for 5 to 10% of diagnosed DM.

Type 2 DM, which most often is diagnosed in adults, is far more common than Type 1 DM. In the western world, it constitutes approximately 90% of all cases of diabetes. In 1994, WHO data indicated a prevalence of approximately 100 million affected individuals and that in a 15 years period this number will increase to more than 250 million.

2.1.3. Management

The treatment of diabetes mellitus with insulin has been established for many decades. It is a life-saving treatment for patients with Type 1 DM and is required by many patients with Type 2 DM.

Effective treatment of diabetes relieves the symptoms of hyperglycaemia and improves general well-being, whereas strict glycaemic control prevents or delays the development of acute and long-term microvascular complications (e.g. retinopathy, nephropathy, and neuropathy) in Type 1 DM and Type 2 DM.

2.2. About the product

Treatment with exogenous insulin has been used since 1922. Different formulations exist, which result in different pharmacokinetic properties. Actrapid is fast-acting, whereas Insulatard® is long-acting and Ultratard is very long-acting. No single standard exists for pattern of administration of insulin and treatment plans vary from physician to physician, for individual patients. Accordingly, insulin requiting diabetic patients can use a variety of different regimens to treat their diabetes. They can either use long- or very long-acting insulin once or twice daily at morning and/or at evening. Fast-acting insulin can be added to these injections in the morning and the evening to deal with the glucose load in response to the breakfast or evening meal. In an even more intensified regimen fast-acting insulin is given at each main meal and very long- or long-acting insulin are given either at bedtime alone or both at breakfast and bed-time. Some patients are treated with continuous subcutaneous insulin infusion

using an insulin pump where fast-acting buffered insulin e.g. Velosulin is administered on a continuous basis with bolus administration at meals.

Two controlled landmark studies; Diabetes Control and Complication Trial (DCCT), and the United Kingdom Prospective Diabetes Study (UKPDS), confirmed what had long been suspected, namely that intensified insulin therapy with near-normalisation of blood-glucose is critical to reduce the risk and postpone the development of late diabetic micro - and macrovascular complications in both Type 1 and Type 2 DM patients. Accordingly, insulin is not only a life-saving drug but also a requisite to reduce the risk of vascular complications seen in long-term diabetes mellitus and recommended as the ultimate therapy for DM in all existing internationally accepted guidelines for diabetes care.

The Applicant is producing Human Insulin by a method employing rDNA technology by fermentation an insulin precursor using Saccharomyces Cerevisiae (baker's yeast) as the production organism. Saccharomyces Cerevisiae exports the correctly folded insulin precursor that is converted and purified to human insulin of mono-component quality.

Insulin circulates in the blood as free monomer and its volume of distribution approximates the volume of extra cellular fluid. The half-life of insulin in plasma is about 5-6 minutes. Degradation of insulin occurs primarily in the liver, kidney and muscle to a less significant degree. Severe impairment of renal function appears to affect the rate of disappearance of free insulin to a greater extent than does hepatic disease.

2.3. Type of Application and aspects on development

Insulatard® was approved in 1988 in the European economic area using the concertation procedure and later transferred to the mutual recognition system.

The reason for the application via the Centralised Procedure in September 2001 was a later introduction of a new expression system for the active substance. In accordance with Commission Regulation (EC) No. 541/95 such a change necessitated a new application which should be approved through the Centralised Procedure. To facilitate the proposed change, Novo Nordisk A/S therefore wished to transfer Insulatard® from the Mutual Recognition Procedure to the Centralised Procedure.

Insulatard® is a genetically engineered intermediate-acting human insulin and has been widely used (please refer to the figures on patient exposure from post-marketing data below).

The clinical documentation in the marketing authorisation application (MAA) via the Centralised Procedure was chosen from 5 sources of clinical studies and data:

- Recent performed studies where Insulatard® has been used as comparator in clinical trials that are performed to demonstrate efficacy and safety for substances under development i.e. Insulin Detemir and Biphasic Insulin Aspart.
    - NN304-1038: Multi-centre, open, randomised, crossover trial to compare the blood glucose lowering effect of NN304 with NPH insulin in type 1 diabetic subjects.
    - NN304/DCD/006/D: A multicentre, uncontrolled open, titration study of the new long/intermediate acting insulin analogue NN304 in a basal/bolus regimen in type 1 diabetic patients.
    - Bi-Asp-1069: A multinational, randomised, controlled double-blind, parallel group efficacy and safety comparison of twice daily biphasic insulin aspart 30 or human NPH insulin in subjects with type 2 diabetes.

- INS/UK/002/UK: An open, randomised, cross-over study to compare twice daily intermediate acting insulin (Human Insulatard®) and once daily long-acting insulin (human Ultratard®) in non-insulin dependent diabetic subjects.

- Studies that were part of the Expert Report on the clinical documentation in the application for product authorisation dated 13.10.87. These studies were done to demonstrate efficacy and safety of genetically engineered human insulin (Insulin HM (ge)) as compared to semi synthetic produced human insulin (Insulin HM (ss)) with particularly clinical and laboratory assessments of direct toxicity, and immunisation or allergy caused by possible contaminants.
- Studies that were part of the clinical expert report in the "Renewal of Marketing Authorizations" dated 18.6 1993.These were mainly Novo Nordisk clinical trials with human insulin that were reported in the period between the two above applications. These studies were mostly addressing transfer from Insulin HM (ss) to insulin HM (ge), pharmacokinetic properties, and use of NovoLet a.o. In total 79 studies were included in this 5-year update.
- Data from periodic safety update reports.
- Publications that have general relevance for this application

The purpose of this application is to get an assessment of a proposed update to the storage conditions for Insulatard® in order to further facilitate the use of the product in relevant countries with challenging temperature conditions and limited access to refrigeration. It is important to emphasize that the product included in the present application is identical to the currently approved product in the EU, apart from the proposed update to the storage conditions.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as suspension for injection in a vial containing 10 ml insulin human equivalent to 1,000 international units (IU); suspension for injection in a cartridge containing 3 ml insulin human equivalent to 300 IU and suspension for injection in a pre-filled pen containing 3 ml insulin human equivalent to 300 IU. These presentations have identical composition. For all presentations 1 ml solution contains 100 IU insulin human (equivalent to 3.5 mg).

Other ingredients are zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), protamine sulfate and water for injections.

The product is available as follows: Insulatard® in a vial (type 1 glass) closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap containing 10 ml of suspension; Insulatard® Penfill® in a cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of suspension; Insulatard® FlexPen® in a cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of suspension in a pre-filled multidose disposable pen made of polypropylene.

2.4.2. Active Substance

2.4.2.1. General information

The active substance of Insulatard® is insulin human (rDNA), which is an International Non-proprietary Name (INN). Insulin human complies with the Ph. Eur. Monograph. It is produced is produced in Saccharomyces cerevisiae by recombinant DNA technology.

2.4.2.2. Manufacture, characterisation and process controls

The Novo Nordisk manufacturing sites of insulin human are located in Kalundborg and Bagsværd, Denmark.

Description of manufacturing process and process controls

The human insulin active substance manufacturing process has been adequately described. The manufacturing process consists of a fermentation step, recovery process and a purification process.

The recovery process, which begins with the concentration of the precursor-insulin from the fermentation broth, proceeds through the enzymatic cleavage of the precursor-insulin, and results in the delivery of the frozen precipitate of the desB30-insulin, for the initiation of the purification of the insulin active substance.

The subsequent steps in purification (including modification) ends up with the purified active substance, insulin human.

Control of materials

The current insulin human *Saccharomyces cerevisiae* production strain is named yAK729.6.16.29/2.3-Δamp and is a transformant of the parental host cell strain MT663. The parental strain MT663 originates from Novo Nordisk A/S and is identical to the parental cell used to generate the Initial Cell Clone (ICC) (MT748) for the insulin human MT748 manufacturing process. The transformed strain was identified and found to be pure, and no contaminating cells were observed.

The cell banking system of master cell bank (MCB) and working cell bank (WCB) is explained and characterisation of MCB and WCB is reported. Stability results of MCB and WCB are available, and the results comply with the specification acceptance criteria for the MCB and WCB.

The cell banking system is appropriately characterised, and it was shown that the identity, purity, and genetic stability of this cell bank system is satisfactory. The WCB is a suitable starting point for the consistent production of precursor-insulin throughout the fermentation process. Moreover, the applicant showed that the cell bank system is stable during storage at -80°C.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

Acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Control of critical steps and intermediates

The applicant performed experimental studies to identify critical parameters and provide evidence of proper parameter intervals for the fermentation, recovery and purification process aiming at a consistent production of active substance.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity, are described for each step. The control of the active substance manufacturing process is considered acceptable.

The stability of three production scale batches of each intermediate stored at -18°C ± 2°C has been studied and confirmed.

Process validation

To validate and evaluate the NN729 (current), NN729 (optimized) and modified process, the following studies have been performed:

- Validation of the NN729 (current), NN729 (optimized) process, and modified process
- Evaluation of impurity removal by the NN729 (current), NN729 (optimized), and modified process
- Comparison of carbon source in NN729 fermentation

The active substance manufacturing process has been validated adequately. Consistency in production has been shown. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces the active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

The first-generation of the manufacturing process (MT748) was based on a *Saccharomyces cerevisiae* strain which is not used for production anymore. The second-generation manufacturing process (NN729 current and optimized) is based on a NN729 strain providing an improved fermentation yield. The latest manufacturing process (modified) contains modifications to the purification process to simplify the process and reduce manual handling.

The applicant characterised the NN729 (current) process by increased fermentation yield, while the genetic stability, removal of common product and process related impurities were similar to the MT748 process. Moreover, new process related impurities were efficiently reduced and consistency in the active substance production was observed according to the specification.

Based on the comparability results, the applicant demonstrated that the NN729 (current) process is fully comparable with the MT748 process, producing an active substance with an impurity profile similar to that of the active substance from the MT748 process.

The aim of the optimization of the NN729 process was to combine the high yielding NN729 strain in fermentation with the recovery and purification processes used in the MT748 insulin human production facilities. The two processes were compared for their ability to remove impurities. Based on the results, the applicant concludes that the NN729 (optimized) process is comparable with the NN729 (current) process, producing an active substance with an impurity profile similar to that of the active substance from the NN729 (current) process.

Also, the physico-chemical properties of insulin human NN729 (current) and MT748 were demonstrated to be comparable, which was also seen between insulin human NN729 (optimized) and NN729 (current).

Characterisation

Structural characterisation and elucidation of the physico-chemical properties of Insulin Human have been performed. The applicant confirmed the theoretical and expected structure of insulin human active substance produced by the NN729 (current and optimized) processes.

The impurities and their control strategy were adequaltey discussed and considered acceptable.

2.4.2.3. Specification

The specification of insulin human complies with the Ph.Eur. monograph and all analytical procedures are Ph.Eur. methods. The specifications are appropriate for this type of the active substance, and they include the following parameters: identification A by assay (Ph. Eur), identification B by peptide mapping (Ph. Eur), high molecular weight proteins (Ph. Eur), related proteins (Ph. Eur), zinc (Ph. Eur), loss on drying (Ph. Eur), sulphated ash (Ph. Eur), microbial control (Ph. Eur), bacterial endotoxins (Ph. Eur) and assay (Ph. Eur).

The analytical release results of insulin human batches are all within the acceptance criteria.

2.4.2.4. Stability

The shelf-life of the active substance is 60 months at -20°C ± 5°C. The stability studies included batches of insulin human manufactured by the modified process, NN729 optimized and MT748 processes stored at long-term conditions at -20°C ± 5°C / -18°C ± 2°C and at accelerated conditions at +5°C ± 3°C. The stability specification limits were met at the long-term storage condition confirming that the active substance is stable within the shelf-life. Moreover, a comparable degradation profile was observed for insulin human produced by the different manufacturing processes.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The Insulatard® finished product is a sterile multidose, cloudy, white suspension. This application (art. 58) concerns the 100 IU/ml strength. It is designed for protracted action.

The composition of the current Insulatard® product (rDNA origin) has not been changed since the development in the 1980's. Hence the same formulation has been used in all clinical studies hereafter.

The protracting effect of protamine on insulin was originally discovered in 1936. The concept was improved in 1946 through the development of isophane insulin, whereby zinc ions (together with phenol and/or metacresol) were used to form an insulin-protamine complex at neutral pH. In the 1970s, mono-component porcine and bovine insulin based Insulatard® formulations were developed and in the 1980s, the equivalent mono-component human insulin containing Insulatard® product was developed. In 1987, in association with development of the NovoPen® dispensing system, the product stability was improved. Sterilisation by filtration is justified given the heat sensitivity of the active ingredient.

Compatibility of the container components and product is shown to be satisfactory. The following container closure systems are included in the application: a 10 ml vial (type 1 glass) closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap containing 10 ml of suspension; Insulatard® Penfill® in a cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of suspension; Insulatard® FlexPen® in a cartridge

(type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of suspension in a pre-filled multidose disposable pen made of polypropylene. The material complies with Ph. Eur. and EC requirements. The choice of the container closure systems has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

Insulatard® is manufactured at five different manufacturing sites: Bagsværd in Denmark, Clayton in US, Montes Claros in Brazil, Chartres in France, and Tianjin in China.

An overview of the processes and critical production parameters is provided and considered satisfactory.

Validation data, including Insulatard® products manufactured at different sites and in different batch sizes, show a consistent, well-controlled manufacturing process.

2.4.3.3. Product specification

The finished product specifications for insulin human (Insulatard®) contains parameters defining identity, content, potency and purity of the product.

In addition to monograph tests, the product is tested by in-house methods for identity and content of preservatives, isophane ratio, and for dose accuracy (FlexPen® only). Full methodologies have been provided for in-house methods as well as complete validations of the tests.

Batch analysis data was provided for batches of each presentation produced at the five different manufacturing sites. Comparable and satisfactory results were shown between each manufacturing site.

It is recommended that a risk assessment on potential presence of elemental impurities in the finished product in line with the ICH Q3D Guideline for Elemental Impurities is performed **(recommendation).**

The provided risk evaluation confirms that there is no risk of nitrosamine presence for the Insulatard® finished product.

The Applicant provided a valid certificate on the Quality Management System, since the FlexPen® is a medical product incorporating a medical device as an integral part. As no changes are introduced to the currently authorised FlexPen® for this application, the submitted results of the FlexPen® assessment of compliance with relevant General Safety and Performance Requirements (GSPR) set out in Annex I of Regulation (EU) 2017/745, are considered acceptable as MDR Article 117 compliance documentation.

2.4.3.4. Stability of the product

Stability reports are provided covering the different Insulatard® presentations, production sites, changes to manufacturing process and container-closure system, and in-use situation. Results have been generated by validated, stability-indicating methods and indicate satisfactory stability. The results support the already approved shelf-life for Insulatard® of 30 months at 5°C and in-use storage condition of 6 weeks at 30°C for the Penfill®/FlexPen® presentations and 4 weeks at 30°C for the vial presentations.

In this application (art. 58), Novo Nordisk proposed an optional storage time and condition before use (4 weeks below 30°C) to meet the request from humanitarian actors of an alternative use of

Insulatard® under challenging temperature conditions in relevant non-EU countries with limited access to refrigeration. The Applicant evaluated this alternative storage period and condition using long-term stability data batches of Insulatard® product, which were representative of the commercial product. To account for the storage period of 4 weeks below 30 °C before use, Novo Nordisk proposed to shorten the maximal shelf life with 6 months from 30 months to 24 months. The stability profile after a storage period of 24 months at 2-8 °C was included as a baseline for the evaluation of the storage at increased temperature (below 30 °C) for an additional 4 weeks.

The Applicant provided a post-approval stability protocol and stability commitment on the proposed optional storage condition before use, which will appropriately address the quality of Insulatard® after storage at the proposed optional condition before use (2-8°C for 24 months followed by 4 weeks at 30°C). In addition, the applicant has committed to perform in-use stability testing on one batch of Insulatard® 10 ml vial, 100 IU/ml and one batch of Insulatard® 3 ml cartridge, 100 IU/ml, after the samples have been stored at the optional storage condition. According to the applicant the results from these studies should be submitted along with a summary of the results (**recommendation**).

2.4.3.5. Adventitious agents

No raw materials of animal derived origin are being used in any steps in the establishment of cell banks.

Since yeast is not the natural host for mammalian viruses, no testing for endogenous or adventitious viruses were performed. The lactose manufacturing process includes heat treatment, which would inactivate most viruses.

Insulin human is tested adequately for bacteria and fungi. Due to the nature of the insulin human fermentation process, no testing for mycoplasma is required.

Based on the safety evaluation, the insulin human is considered safe with regards to TSE/BSE and virus.

2.4.4. 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 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.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to submission of data from an in-use stability study with batches stored at the optional storage condition in order to confirm the quality of Insulatard® after a combined storage period at the proposed optional storage condition and in-use condition, and to the lack of a risk assessment on potential presence of elemental impurities in the finished product in line with the ICH Q3D. These points are put forward and agreed as recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations 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:

It is recommended that a risk assessment on potential presence of elemental impurities in the finished product in line with the ICH Q3D Guideline for Elemental Impurities is performed.

The applicant has committed to perform an in-use stability test on one batch of Insulatard® 10 ml vial, 100 IU/ml and one batch of Insulatard® 3 ml cartridge, 100 IU/ml, after the samples have been stored at 24 months at 2-8°C and 4 weeks at 30°C ("optional storage condition"). According to the applicant the results from these studies are expected no later than 01 November 2024 and these should be submitted along with a summary of the results.

2.5. Non-clinical aspects

2.5.1. Introduction

Insulin HM(ge) has been proven to be chemically identical to insulin HM(ss) and authentic human insulin. Porcine and bovine insulin have been marketed since the early 1920s, and later the HM(ss) was marketed. In the early 1980ies it became possible to produce insulin HM(ge) by recombinant DNA technology. In the pre-clinical testing a number of studies were carried out, which showed no difference between the marketed insulin HM(ss) and insulin HM(ge). Insulin HM(ge) has been marketed since 1988 under the product name Actrapid and is the same active substance as in Insulatard®. It is therefore considered to be a well-known drug with long-term marketing experience.

Insulatard® manufactured by use of recombinant DNA technology was originally approved in EU under the Concertation Procedure in 1988 and was transferred to the Centralised Procedure in 2002. The non-clinical development programme was therefore conducted before introduction of the CTD structure.

The Toxico-Pharmacological Expert Report included in the present application was first provided when Insulatard® was approved in the EU via the Centralised Procedure in 2002 (EMEA/H/C/000441). No further non-clinical data or information have been submitted for Insulatard® in the context of this application under Article 58 of Regulation (EC) 726/2004.

All studies supporting the initial approval of Insulatard® were conducted in accordance with Good Laboratory Practice (GLP) except for the primary pharmacology studies, for which GLP was not required. Additional data presented in the form of published papers or reports from academic institutes do not contain information with regard to GLP status.

The purpose of this application is to get an assessment of a proposed update to the storage conditions for Insulatard® in order to further facilitate the use of the product in relevant countries with challenging temperature conditions and limited access to refrigeration. It is important to emphasize that the product included in the present application is identical to the currently approved product in the EU, apart from the proposed update to the storage conditions.

2.5.2. Pharmacology

Insulatard® is a suspension of the intermediate acting insulin HM(ge)-protamine complex (human isophane insulin NPH). Insulin HM(ge) is synonymous for human insulin obtained by recombinant DNA technique. Insulatard® contains insulin mixed with another substance, protamine, in an 'isophane' form which is absorbed much more slowly during the day. This gives Insulatard® a longer duration of action.

The biological activities of insulin are well known, and therefore the main purpose in the original study programme for primary and secondary effects was to demonstrate the similarity between the new insulin HM(ge) (genetically engineered human insulin) and marketed semi synthetic variant HM(ss). The approach was concentrated on quantitative assays of hypoglycaemic activity and potency.

As the active component of Insulatard® is similar to Actrapid HM(ge), no new specific pharmacodynamic studies in vitro or in laboratory animals have been provided for this application. The non-clinical programme includes studies performed in the eighties demonstrating the similarity between recombinant insulin human and semi-synthetic insulin human, later studies supplementing above studies and more recent studies where insulin human (rDNA) was used as a reference substance for insulin analogues.

2.5.2.1. Primary pharmacodynamic studies

No new studies have been submitted. The existing data from the original Insulatard® MAA together with clinical data confirming the proof-of-concept in diabetes, is sufficient for this procedure.

2.5.2.2. Secondary pharmacodynamic studies

No studies have been provided. The lack of any specific secondary pharmacology studies is accepted based on the long-term clinical use of Insulatard®.

2.5.2.3. Safety pharmacology programme

An extended program of safety pharmacology studies including core battery safety pharmacology studies performed for insulin HM (ge) was submitted as part of the initial MAA. No specific hazards were identified. Due to the extensive clinical experience with insulins, including Insulatard®, no new safety pharmacology studies are warranted for this article 58 procedure.

2.5.2.4. Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were provided. This is acceptable due to the extensive clinical experience with the product.

2.5.3. Pharmacokinetics

No specific pharmacokinetic studies were submitted in the original MAA for Insulatard®. As no new non-clinical studies are submitted with the current art. 58 application, no dedicated non-clinical pharmacokinetic studies are available. However, no new non-clinical studies are deemed necessary for the current article 58 procedure, as extensive clinical PK data are available for Insulatard® that supersedes the need for new non-clinical data.

2.5.4. Toxicology

No specific studies were conducted on the toxicity of Insulatard for the purpose of the current article 58 application. However, some experiments where isophane insulin NPH (=Insulatard®) was used as a reference substance to the testing of the insulin detemir (NN304) were provided in the original MAA for Insulatard®. Toxic effects were related to hypoglycaemia.

The available – although limited - toxicology studies are considered sufficient to support the current article 58 procedure. Together with extensive clinical safety data on insulins through more than 30 years of marketing, no additional non-clinical studies are required for an already marketed medicinal product.

2.5.4.1. Single dose toxicity

No dedicated single dose toxicity studies with Insulatard® are available.

In mice and rats at dosages up to 4000 U/kg insulin HM(ge) (same active substance as in Insulatard®), no treatment related signs apart from few sporadic hypoglycaemic reactions were seen.

2.5.4.2. Repeat dose toxicity

No dedicated repeat dose toxicity studies with Insulatard® are available.

In a 4-week SC study of insulin HM(ge) (same active substance as in Insulatard®) in rats, doses up to 200 U/kg/day resulted in cases of hypoglycaemic deaths at 200 U/kg. High dosages of insulin HM(ss) as well as insulin HM(ge) lowered protein plasma concentration, and a slightly lowered urea and increased blood glucose was also seen. No difference was seen between animals treated with insulin HM(ss) and insulin HM(ge).

In dogs treated for 13 weeks with insulin HM(ge) (same active substance as in Insulatard®), up to 3 U/kg/day was given SC. Clinical signs at 1 U/kg and 3 U/kg was peripheral vasodilatation, and at 3 U/kg ocular discharge and quiet behaviour. Body weight and food consumption was slightly increased. All effects were attributed to the hypoglycaemic state.

Two newer studies used insulin HM(ge) (same active substance as in Insulatard®) as a reference at the highest dose level:

In a 52-week study in rats, 100 U/kg/day was given SC. Dosage was lowered to 75 U/kg/day from week 38 because of many sudden deaths, apparently caused by hypoglycaemia. Body weight gain and food consumption was increased. Triglyceride levels were increased at the highest dose. At the highest dose, there was an increased level of mammary gland cysts and mammary gland tumours were found, but the incidence of mammary tumours was not different from the controls.

In a 52-week study in dogs, 1 U/kg/bid was given SC. Treatment was changed to once daily SC because of hypoglycaemic episodes and one death. One dog had abnormal weight gain. There were no other findings considered to be of toxicological significance.

2.5.4.3. Genotoxicity

In the original MAA, the following studies were conducted and were all negative for mutagenic potential:

- The Ames test with and without metabolic activation (doses up to 400 µg/plate),

- The *in vitro* chromosomal aberration test in human peripheral lymphocytes with and without metabolic activation (doses up to 80 µg/ml),
- A test for induction of gene mutations in Chinese Hamster V79 cell line with and without metabolic activation (doses up to 80 µg/ml),
- The micronucleus test in mouse bone marrow erythrocytes (a single dose of up to 4000 U/kg).

Insulin HM(ge) was additionally used as a reference substance in a later study on gene mutations in mouse lymphoma L5178Y cells (5-trifluorothymidine resistance). The study was done with and without metabolic activation (doses up to 5000 µg/ml). This study also proved negative for mutagenicity.

It could be considered if new or additional studies of genotoxicity should be performed for the current procedure, as new guidance in this area was implemented with the ICH M7 guideline. The studies supporting the original application for Insulatard® are of course of older date. However, as none of the original studies on genotoxicity raised any concerns for safety, and the many years of clinical use of insulins have not raised concerns in this area, the original studies are considered sufficient for this article 58 procedure for an already marketed product.

2.5.4.4. Carcinogenicity

Potential carcinogenicity of insulin HM(ge) (same active substance as Insulatard®) has been investigated in long-term rat and dog studies. Increased incidence of mammary tumours was seen in rats, but not in dogs. The effect in rats was deemed to be caused by mitogenic and growth-promoting action via the insulin receptor, but probably also related to the fact that Sprague Dawley rats are especially sensitive and were given large doses.

There was no increase of mammary gland hyperplasia or tumours in the 12-month dog study, supporting a rat-specific finding for this effect.

The human epidemiological literature was reviewed in late 1990s (Friis and Dideriksen, 1999) for evidence of association between diabetes mellitus treatment with insulins and cancer in humans. A possible link between insulin treatment and breast cancer has been investigated in three case control and three cohort studies. No association was documented at that time. As the product is the same as the one marketed since 1988, the non-clinical studies from the original MAA for Insulatard® are considered sufficient for the current article 58 procedure.

2.5.4.5. Reproductive and developmental toxicity

Reproduction toxicity studies were not conducted for the original MAA for Insulatard®, as insulin is known to have teratogenic potential. However, in the preclinical programme for insulin aspart, a full battery of reproduction toxicity experiments was conducted according to ICH guidelines. Actrapid was used as a reference substance, which has the same active substance as Insulatard®. These data are therefore considered valid and relevant for this assessment. The noted effects on embryos and foetuses were only seen at severe maternal hypoglycaemia and are already known to occur in incorrectly treated diabetic women.

Please also refer to the clinical section below on effects of insulin to pregnant woman and the unborn child, as well as the information in SmPC section 5.3.

Clinical data from years of use of Insulatard® has not raised additional concerns on this matter and for this article 58 procedure, no additional non-clinical reproductive toxicology studies are warranted.

2.5.4.6. Toxicokinetic data

Toxicokinetic studies were conducted during the 'newer' 52-week studies with insulin HM(ge) (same active substance as in Insulatard®) in rats and dogs and during the segment II test in pregnant rabbits. Linearity for plasma levels in relation to dose was demonstrated for both insulins. Cmax for these insulins was comparable. Elimination rate did not change with time.

No new non-clinical studies are deemed necessary for the current article 58 procedure, as insulins have extensive clinical PK data that supersedes the need for new non-clinical data.

2.5.4.7. Local Tolerance

No quality changes to the formulation are made and therefore, no new non-clinical tolerance studies are required for this procedure. Also, the clinical experience with Insulatard® through decades supersedes the need for non-clinical data.

2.5.4.8. Other toxicity studies

No dedicated studies performed. Insulatard® has low potential to induce insulin antibodies and therefore the risk of immunotoxicity is considered low. There are no safety concerns as to the impurities given the limits described in the specifications of the tests.

2.5.5. Ecotoxicity/environmental risk assessment

A joint Environmental assessment report for Actrapid®, Insulatard®, Mixtard® and Velosulin® dated 2004.01.08 was submitted. In this report it was concluded that the PECsurfacewater did not exceed the threshold of 0.01µg/L.

However, a more recent justification for not performing any ERA studies has also been submitted (dated 31 March 2009). In this justification the following is stated:

The amendment to the extension application has not changed the active drug substance so the Environmental Risk Assessment from January 2004 is still valid. The risk assessment was in accordance with the draft discussion paper on environmental risk assessment of non-genetically modified organism (non-GMO) containing medicinal products for human use from the European Agency for the Evaluation of Medicinal Products (EMEA, 2001).

In 2006 the EMEA's guideline "Guideline on the environmental risk assessment of medical products for human use" came into effect. According to this guideline substances like vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment.

Insulin human is a protein consisting of natural amino acids.

On this basis it is concluded that insulin human is exempted from EMEA's guideline and it is therefore not necessary to perform an environmental risk assessment of insulin human.

Thus, the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Insulatard® is not expected to pose a risk to the environment. Furthermore, PEC surfacewater value is below the action limit of 0.01 µg/L.

2.5.6. Discussion on non-clinical aspects

Insulatard® is a suspension of the intermediate acting insulin HM(ge)-protamine complex (human isophane insulin NPH). Insulin HM(ge) is synonymous for human insulin obtained by recombinant DNA technique. Insulatard® contains insulin mixed with another substance, protamine, in an 'isophane' form which is absorbed much more slowly during the day. This gives Insulatard® a longer duration of action.

The biological activities of insulin are well known, and therefore the main purpose in the original study programme for primary and secondary effects was to demonstrate the similarity between the new insulin HM(ge) (genetically engineered human insulin) and marketed semi synthetic variant HM(ss). The approach was concentrated on quantitative assays of hypoglycaemic activity and potency.

As the active component of Insulatard® is similar to Actrapid HM(ge), no new specific pharmacodynamic studies in vitro or in laboratory animals have been conducted for this application. The non-clinical programme includes studies performed in the eighties demonstrating the similarity between recombinant insulin human and semi-synthetic insulin human, and later studies supplementing these studies and more recent studies where insulin human (rDNA) was used as a reference substance for insulin analogues.

The pharmacodynamic studies in vitro and in vivo reflect the studies presented in the original MAA for Insulatard® and support the proof-of-concept for the mode of action of Insulatard®. Together with the extensive clinical data obtained from use of the product over decades, the evidence of pharmacodynamic effects (proof-of-concept) of the product is well known.

An extensive safety pharmacology program was performed for the MAA of human insulin HM(ge) = Actrapid), and these studies are still considered valid, together with the available clinical safety data through years' of clinical use.

No new non-clinical pharmacokinetic data are provided, but this is superseded by available clinical PK data, so considered acceptable.

The toxicology studies cited were performed in the late 1980s and a few additional studies in late 1990s. The studies support clinical use of Insulatard®. Post-marketing data supersede the need for new toxicology studies.

Potential carcinogenicity of insulin HM(ge) (same active substance as Insulatard®) has been investigated in long-term rat and dog studies. Increased incidence of mammary tumours was seen in rats, but not in dogs. The effect in rats was deemed to be caused by mitogenic and growth-promoting action via the insulin receptor, but probably also related to the fact that Sprague Dawley rats are especially sensitive and were given large doses. There was no increase of mammary gland hyperplasia or tumours in the 12-month dog study, supporting a rat-specific finding for this effect.

The human epidemiological literature was reviewed in late 1990s (Friis and Dideriksen, 1999) for evidence of association between diabetes mellitus treatment with insulins and cancer in humans. A possible link between insulin treatment and breast cancer has been investigated in three case control and three cohort studies. No association was documented at that time. As the product is the same as the one marketed since 1988, the non-clinical studies from the original MAA for Insulatard® are considered sufficient for the current article 58 procedure. All were negative for mutagenic potential.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Insulatard® is not expected to pose a risk to the environment. Furthermore, PEC surface water value is below the action limit of 0.01 µg/L.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical data for this article 58 procedure are identical to the data submitted with the original MAA for Insulatard® in 2001. The product is identical (no quality changes) to the already approved Insulatard® product. No new non-clinical data has been submitted or discussed by the Applicant for this procedure.

Due to the extensive clinical use of Insulatard® and the wide knowledge on safety and efficacy of insulins which have been used for decades, no new non-clinical studies are warranted for this application. The product is already approved in more than 140 countries and no quality changes are introduced in this procedure, so from a non-clinical point of view, the benefit/risk is positive.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

Studies undertaken

Three pharmacodynamic and/or pharmacokinetic studies provide the basis for the assessment of the pharmacodynamic and pharmacokinetic properties of Insulatard®. All studies included healthy subjects only.

Study NN304/DCD/001/D

This was a single-centre, open-label, randomised, 5-period crossover trial to investigate the pharmacokinetic and pharmacodynamic properties of NN304 (=insulin detemir) at ascending dose levels in comparison to human NPH-insulin during euglycaemic clamps in healthy male volunteers.

11 healthy subjects were given single doses of Insulatard® (NPH insulin) 0.3 U/kg (two trial days), and insulin detemir 0.15, 0.3 and 0.6 U/kg on separate study days. The medication was administered as subcutaneous injections in the abdominal wall. During each study period (2 h before and 24 h after injection), the blood glucose level was clamped at 5 mmol/l, and the subjects remained fasting.

Regular insulin was infused intravenously at a rate of 0.15 mU/kg/min to suppress endogenous insulin production. Blood glucose, insulin levels, C-peptide levels and glucose infusion rate values were obtained for the 24-h period after injection.

Study NN304/DCD/4/A

This was a single-centre, double-blind, randomised, placebo-controlled, 5-period crossover trial to investigate the pharmacokinetic and pharmacodynamic properties of NN304 in comparison to human NPH-insulin during euglycaemic glucose clamps in healthy male volunteers. The design of this study was very similar to the one in Study NN304/DCD/001/D. However, the clamping technique was somewhat different, and placebo treatment was included in the study.

10 healthy subjects were given single doses of Insulatard® (NPH insulin) 0.3 and 0.6 U/kg. The insulins were given as subcutaneous injections in the abdominal wall. During each study period (1 h before and 24 h after injection), the blood glucose level was clamped at 4.5 mmol/l, and the subjects remained fasting. Regular insulin was not infused intravenously in this study. Blood glucose, insulin levels, C-peptide levels and glucose infusion rate values were obtained for the 24-h period after injection.

Study NN304-1028

This was a four-period, comparative, open, randomised, crossover trial in healthy male volunteers investigating the bioavailability of NN304 and NPH-insulin when administered as a subcutaneous injection and relative to intravenous injection.

The aim of this study was to determine the absolute bioavailability of insulin detemir (NN304) and Insulatard® as subcutaneous injections relative to intravenous infusion. In a randomised, crossover design, 16 healthy males were given single doses of Insulatard® (NPH insulin) 0.2 U/kg s.c., Actrapid (human soluble insulin) 0.075 U/kg as a 30-min i.v. infusion, insulin detemir 0.2 U/kg s.c. and insulin detemir 0.01 U/kg as a 30-min i.v. infusion. For safety reasons, the subjects were clamped at their fasting glucose level around 4.5 mmol/l. Blood samples for plasma glucose, total insulin, C-peptide and NN304 were drawn for 12 h after i.v. dosing and 24 h after s.c. dosing.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

Study NN304/DCD/4/A

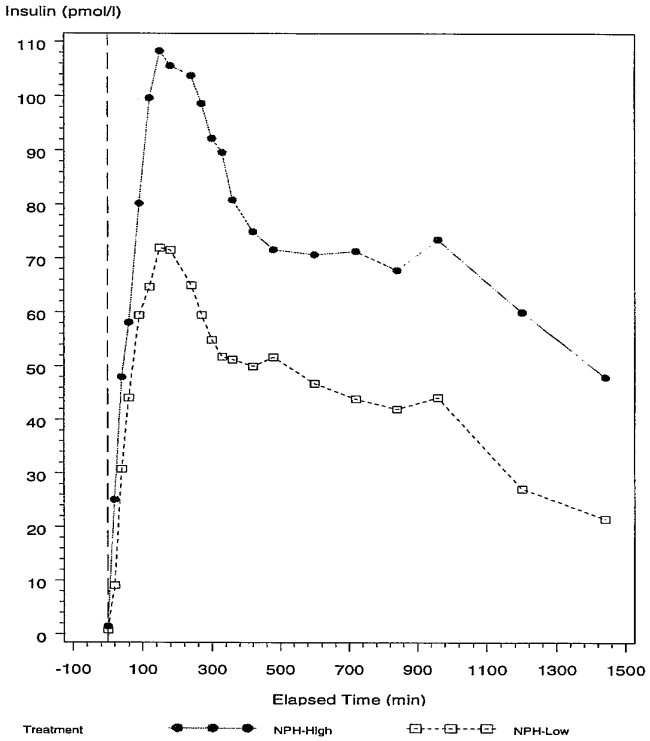
The pharmacokinetic results are presented in the table below. Mean AUC_{0-24} and C_{max} values for exogenous insulin were significantly higher for the high Insulatard® dose as compared to the low dose, approximately 1.7-fold and 1.5-fold, respectively. Mean time to peak concentration was about 5 hours for both doses. The figure below depicts the calculated concentrations of exogenous insulin (NPH insulin) over time. The figure shows that exogenous insulin levels had not returned to baseline levels at the end of the study period.

Table. Summary of Insulatard® results from Study NN304/DCD/4/A.

	NPH-Low	NPH-High
AUC_{0-24} ((pmol/l)*min)		
N	10	10
Mean	60229	101975
SD	20057	31531
Min	22150	62936
Max	90529	163862
C_{max} (pmol/l)		
N	10	10
Mean	80.7	120.3
SD	33.1	45.0
Min	30.0	76.8
Max	147.7	219.7
MRT_{0-24} (min)		
N	10	10
Mean	617.3	686.8
SD	128.3	113.3
Min	418.5	515.7
Max	775.2	921.8
t_{max} (min)		
N	10	10
Mean	321.0	288.0
SD	314.3	322.9
Min	90.0	150.0
Max	960.0	1200.0

Trial ID.: NN304/DCD/004/A
Spadille Biostatistics ApS (tab07.sas/7.asc) 07JAN98
Cross-reference: EOT Table 7.

Figure. Exogenous insulin profiles after Insulatard® (Study NN304/DCD/4/A).



Study NN304-1028

The absolute bioavailability of Insulatard® was estimated to be 49% (confidence interval limits 38-62%) based on an ANOVA analysis of 12 subjects. Other pharmacokinetic results included mean t_{max}, which was about 7 h for Insulatard® administered subcutaneously.

Distribution

No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Elimination

As the half-life of intravenously injected human insulin is relatively short, the terminal half-life of human insulin following subcutaneous injection is a measure of the terminal absorption rather than the elimination of insulin from plasma per se. The terminal elimination half-life of human insulin following s.c. injection of Insulatard® has not been calculated in the listed studies. Trials have indicated a elimination half-life of about 5-10 hours.

Excretion of Insulatard® was not formally investigated. As insulin is eliminated by metabolism, excretion of unchanged drug is minimal or non-existent.

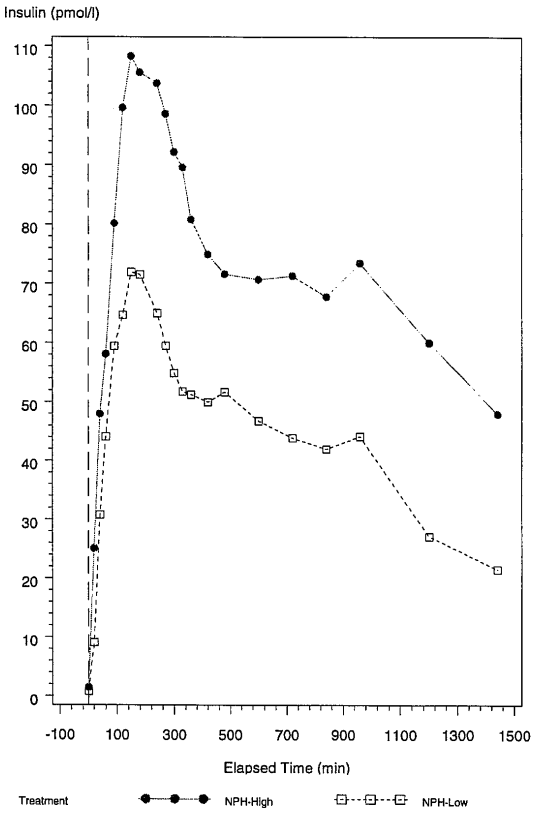
Metabolism of Insulatard® was not formally investigated. From previously published data it is known that various proteolytic enzymes degrade human insulin. The degradation products are inactive. Presumably, the degradation products are broken down to amino acids and metabolised or incorporated into host proteins.

Dose proportionality and time dependencies

Study NN304/DCD/4/A

Dose proportionality was addressed in this study, which included two Insulatard® doses. The results indicate that Insulatard® performs dose-proportionality and follows a 1st order pharmacokinetic model.

Also, blood levels of insulin had not returned to baseline at the end of the study period. Therefore, onset of action is within 1½ hours, reaches a maximum effect within 4–12 hours and the entire duration of action is approximately 24 hours.



Special populations

The Applicant has not submitted any data on the pharmacokinetics in patients with impaired renal/hepatic function. It is known that the liver, the kidneys and the muscles are primary sites of insulin degradation. Renal and hepatic impairment may reduce insulin degradation and thus reduce insulin requirements.

The effect of age was not investigated.

As insulin doses are titrated individually, the lack of PK studies in the mentioned special populations is considered acceptable.

Pharmacokinetic interaction studies

No formal interaction studies have been performed.

Concomitant administration of certain drugs may increase or decrease the blood glucose lowering effect. The mechanisms of these effects are different ones, e.g. by influencing insulin biosynthesis or secretion or changing the sensitivity to insulin of its target tissues.

No formal interactions studies have been conducted. The list of drugs in the SmPC, reducing or increasing insulin requirements, respectively, is based on literature reviews.

2.6.2.2. Pharmacodynamics

Mechanism of action

Insulatard® has blood glucose lowering properties. This is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and the simultaneous inhibition of glucose output from the liver.

Primary and Secondary pharmacology

The figure below (Study NN304/DCD/001/D) depicts the glucose infusion rate (GIR) after administration of Insulatard® 0.3 U/kg. As can be seen, the maximum effect of Insulatard® is observed about 3-6 hours after injection. At the end of the study period, GIR was still well over baseline level.

Figure. Mean GIR profile after NPH treatment (Study NN304/DCD/001/D).

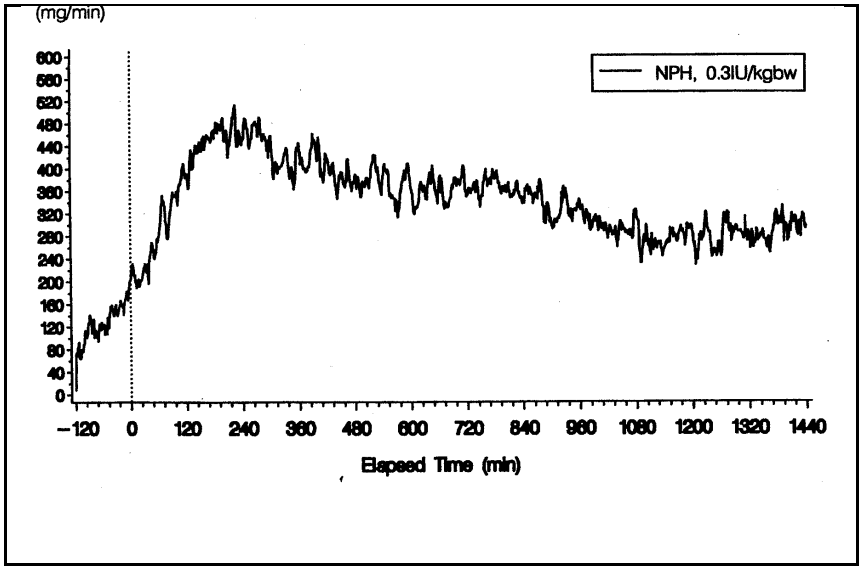


Figure. Glucose infusion rates after injection of Insulatard® (NPH insulin) 0.3 and 0.6 U/kg, insulin detemir 0.3 and 0.6 U/kg, and placebo. (Study NN304/DCD/4/A).

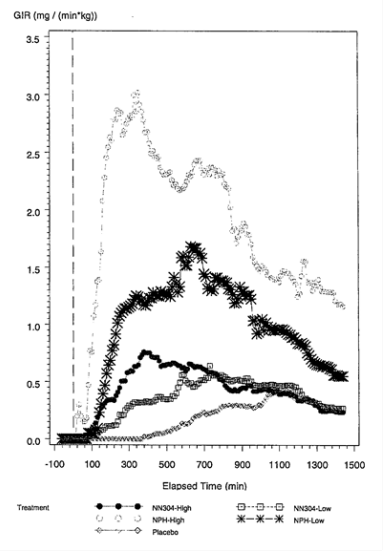


Table. *Summary of pharmacodynamic results from Study NN304/DCD/4/A.*

	Placebo	NPH-Low	NPH-High	NN304-Low	NN304-High
$AUC_{GIR0-24}$ (mg/kg)					
N	10	10	10	10	10
Mean	265.3	1408.4	2670.5	512.4	629.0
SD	251.4	979.9	1960.5	348.8	491.0
Min	0.0	342.0	634.2	0.0	65.4
Max	701.1	3691.1	6690.2	1097.0	1498.3
GIR_{max} (mg/(kg*min))					
N	10	10	10	10	10
Mean	0.5	2.6	4.3	0.8	1.0
SD	0.4	2.5	2.8	0.5	0.6
Min	0.0	0.8	1.0	0.0	0.2
Max	1.3	9.0	10.5	1.6	1.9
$tGIR_{max}$ (min)					
N	7 *)	10	10	9 **)	10
Mean	1060.0	628.4	490.1	702.2	615.0
SD	273.6	253.6	462.8	199.4	372.6
Min	690.0	270.0	23.0	450.0	190.0
Max	1340.0	1030.0	1240.0	1060.0	1150.0
tGIR(50%) (min)					
N	7 *)	10	10	9 **)	10
Mean	1085.2	781.6	744.7	879.0	736.0
SD	141.4	192.1	183.4	178.9	281.7
Min	879.7	473.8	475.5	672.2	340.0
Max	1292.1	1121.0	1063.8	1142.2	1176.0

Trial ID.: NN304/DCD/004/A
* : GIR=0 at all timepoints for 3 subjects
**: GIR=0 at all timepoints for 1 subject
Spadille Biostatistics ApS (tab14.sas/14.asc) 08JAN98
Cross-reference: EOT Table 14.

2.6.3. Discussion on clinical pharmacology

Three PK/PD studies were provided and are described in this assessment, and they perform the basis for the evaluation of the pharmacokinetic and pharmacodynamic properties of Insulatard®. These studies were conducted as part of the clinical development programme for at that time, a new long-acting insulin analogue; insulin detemir, also referred to as NN304. Insulatard® was included as a

comparator, and was not target of the primary analysis. However, the provided results are considered to be valid and to represent the PK properties for Insulatard®.

Onset of action was described to be within 1,5 hours, receiving a tmax within 2-18 hours, and duration of action was calculated to be approximately 24 hours. This is also in line with the statements available in the current SmPC for Insulatard®. Elimination half-life was not determined in the provided studies; however, the presented data suggest an elimination half-life that corresponds to the provided elimination half-life stated in the SmPC for Insulatard® of 5-10 hours.

Metabolism of Insulatard® was not formally investigated, but since Insulatard® is a human insulin (i.e. a peptide hormone, originally produced by beta cell from the pancreatic islets), it is expected that Insulatard® is broken down to amine acids and metabolised as other proteins.

None of the performed clinical studies have addressed the intra- and inter-individual variability. The pharmacokinetic process is influenced by several factors (e.g. insulin dose, injection route and site, thickness of subcutaneous fat, type of diabetes), and the pharmacokinetics of insulin medicinal products are therefore affected by significant intra- and inter-individual variation. Therefore, the dosing of Insulatard® is considered individual, and determined in accordance with the need of the patient. The physician determines whether one or several daily injections are necessary. This is carefully outlined within the current SmPC (section 4.2).

As none of the provided clinical studies investigated the pharmacokinetic properties within special populations or target population (e.g. individuals with diabetes, children, elderly, individuals with impaired renal or hepatic function etc), it is concluded that that the provided results do not reflect the target population or special populations. However, the lack of these studies is considered acceptable as long as the insulin dose is adjusted individually, as recommended in the SmPC.

Finally, there is also a lack of interactions studies. The list of potential interactions stated in the SmPC is endorsed. The listed drugs are primarily products known to interact with glucose metabolism.

Insulatard® has blood glucose lowering properties. This is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and the simultaneously inhibition of glucose output from the liver.

The provided GIR profiles in figures 1 (Study NN304/DCD/001/D) and 2 (Study NN304/DCD/4/A), evaluate the pharmacodynamic effects of Insulatard®. As concluded the maximum effects of Insulatard® was observed after 3.6 hours after injection, and in the end of study period (24 hours), the GIR was still over baseline (and over placebo treatment), suggesting an effect of Insulatard® after 24 hours on glycaemic control.

The provided results correspond to the results for the PK part, and the fact that maximum effect is reached within 4-12 hours (as stated in the SmPC), and that duration of action is approximately 24 hours. It is endorsed that the PD results substantiate the facts concluded from the PK results regarding onset and duration of action. This suggests that there is a relationship between plasma concentration of Insulatard® and effect.

2.6.4. Conclusions on clinical pharmacology

Overall, the pharmacokinetic and pharmacodynamic properties of Insulatard® evaluated in this assessment, support a positive benefit-risk evaluation.

2.6.5. Clinical efficacy

The clinical documentation submitted in the application for the MAA via the Centralised Procedure was chosen from 5 sources of clinical studies and data:

- Recent performed studies where Insulatard® has been used as comparator in clinical trials that are performed to demonstrate efficacy and safety for substances under development i.e. Insulin Detemir and Biphasic Insulin Aspart.
    - NN304-1038: Multi-centre, open, randomised, crossover trial to compare the blood glucose lowering effect of NN304 with NPH insulin in type 1 diabetic subjects.
    - NN304/DCD/006/D: A multicentre, uncontrolled open, titration study of the new long/intermediate acting insulin analogue NN304 in a basal/bolus regimen in type 1 diabetic patients.
    - Bi-Asp-1069: A multinational, randomised, controlled double-blind, parallel group efficacy and safety comparison of twice daily biphasic insulin aspart 30 or human NPH insulin in subjects with type 2 diabetes.
    - INS/UK/002/UK: An open, randomised, cross-over study to compare twice daily intermediate acting insulin (Human Insulatard®) and once daily long-acting insulin (human Ultratard®) in non-insulin dependent diabetic subjects.
- Studies that were part of the Expert Report on the clinical documentation in the application for product authorisation dated 13.10.87. These studies were done to demonstrate efficacy and safety of genetically engineered human insulin (Insulin HM (ge)) as compared to semi synthetic produced human insulin (Insulin HM (ss)) with particularly clinical and laboratory assessments of direct toxicity, and immunisation or allergy caused by possible contaminants.
- Studies that were part of the clinical expert report in the "Renewal of Marketing Authorizations" dated 18.6 1993.These were mainly Novo Nordisk clinical trials with human insulin that were reported in the period between the two above applications. These studies were mostly addressing transfer from Insulin HM (ss) to insulin HM (ge), pharmacokinetic properties, and use of NovoLet a.o. In total 79 studies were included in this 5-year update.
- Data from periodic safety update reports.
- Publications that have general relevance for this application

2.6.5.1. Dose response study(ies)

Not applicable. Insulin is dosed according to monitored blood-glucose levels and intended meal.

2.6.5.2. Main study(ies)

In support of the initial MAA for Insulatard®, the MAH submitted a total of three studies considered as pivotal studies as well as one supportive study. Two studies (also the supportive study) were conducted in patients with Type I DM and two studies were conducted in patients with Type II DM.

These studies are briefly described below.

Studies in patients with Type I Diabetes Mellitus

Trial NN304-1038

This was a multi-centre, open, randomised, crossover trial to compare the blood glucose lowering effect of NN304 with NPH insulin in type 1 diabetic subjects.

Study design

Trial NN304-1038 was a multi-centre, open, randomised cross-over trial. After a 2-weeks run in period the 2 treatment periods of 6 weeks each followed.

Study medication

The test product was NN304, which is a soluble basal insulin analogue (with an expected more stable insulin delivery with less intra-subject variation), and the reference product was NPH insulin 100 IU/ml. Both were to be administered in the evening. HI was administered to the meals.

Study population

Adult patients with Type 1 DM for at least 2 years and being treated according to the basal/bolus regimen were included. Patients with proliferative retinopathy, NPH insulin dosages $\geq$40 IU/d, impaired hepatic or renal function, heart failure according to NYHA class III and IV, unstable angina pectoris or recent myocardial infarction, uncontrolled hypertension, pregnancy were excluded. Patients self-monitored BG and were informed about the BG targets. Sixty subjects were to be included.

Study objective

The primary objective of the trial was to compare the blood glucose lowering effect of NN304 with that of NPH insulin in terms of metabolic control.

Endpoints

Primary endpoints: The primary efficacy endpoint was $AUC_{glu,23-8}$ Secondary endpoints were delta $_{glu,23-8}$, shape of the serum glucose profile in beforementioned time interval, AUC $_{glu,8-12}$, $AUC_{glu,12-22}$, $C_{max(glu,8-12)}$, fructosamine at visits 1, 2, 5, and 8, home monitored FBG on the last 4 days of each treatment period, dose of basal insulin.

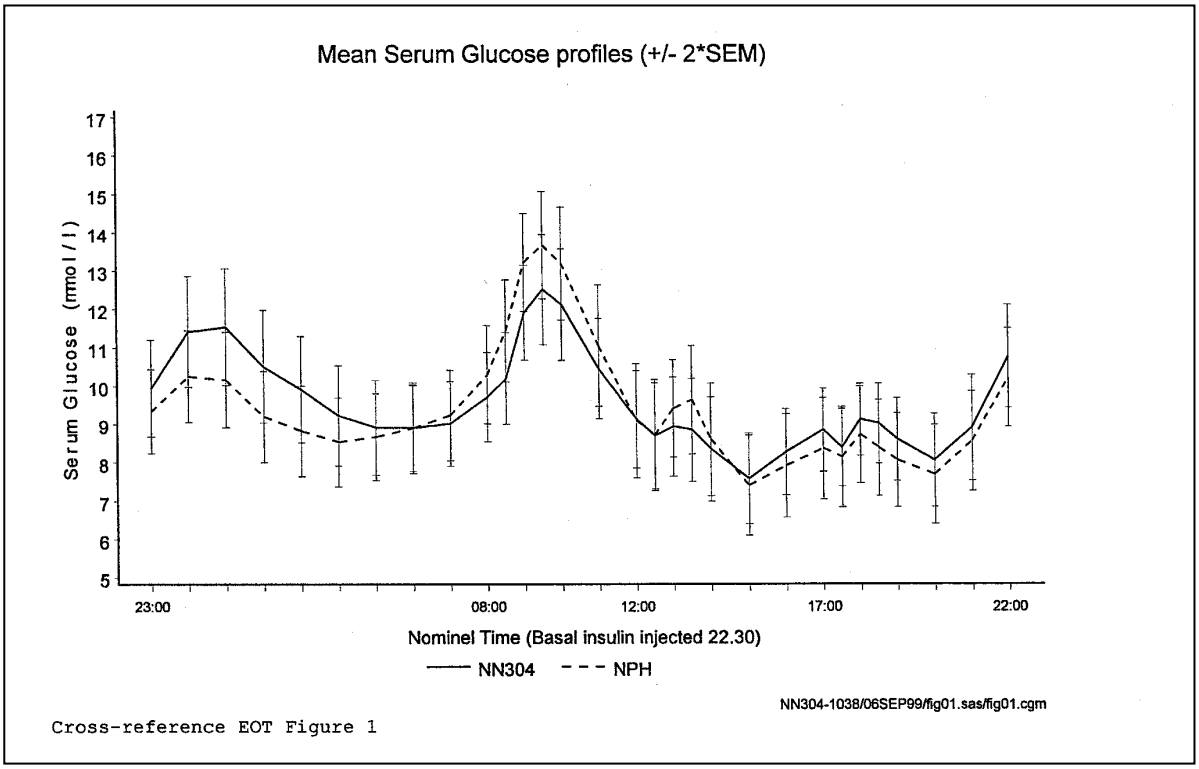
Secondary endpoint: Secondary endpoint derived from the 24-hour serum glucose concentration.

Study results

Study populations: Fifty-nine (59) subjects were randomised, 56 subjects completed the trial. The reasons for premature discontinuation in the 3 subjects were a C-peptide level above the inclusion criteria in 2 cases and 1 patient felt uncomfortable with the volume of NN304 injected.

Efficacy results:

Primary endpoint: $AUC_{glu,23-8}$ was comparable for NPH insulin and NN305, the ratio NN304/NPH was 1.04. The mean serum glucose profiles for the 2 treatments are shown below:



Cross-reference EOT Figure 1

Secondary endpoints: For the secondary endpoints derived from the 24-hour serum glucose concentration–time-curves, no statistically nor clinically relevant difference between the 2 treatments was noted. The intra-and inter-subject variability were lower for NN304, the result reached statistical significance for the intra-subject variability. The fructosamine levels between the treatments were comparable.

The daily dose of NPH insulin in the last seven days of each treatment phase was 0.28 IU/kg (SD 0.09), the total bolus insulin dose in the last 7 days of each treatment phase was 0.42 IU/kg.

Study NN304/DCD/006/D

This was a multicentre, uncontrolled open, titration study of the new long/intermediate acting insulin analogue NN304 in a basal/bolus regimen in type 1 diabetic patients

Objective: The objective of this trial was to gain experience with NN304 in order to find out how to transfer patients on a basal/bolus regimen from NPH insulin once or twice daily to NN304 once daily. During the 2-week run-in period patients were treated with NPH insulin.

Studies in patients with type II Diabetes Mellitus

Study Bi-Asp-1069

This was a multinational, randomised, controlled double-blind, parallel group efficacy and safety comparison of twice daily biphasic insulin aspart 30 or human NPH insulin in subjects with type 2 diabetes

Study design and duration: The trial was a multi-national, randomised, controlled, double-blind parallel group study. The treatment period was 16 weeks followed by 2 weeks follow-up period.

Study medication: Patients were randomised to receive twice daily injections (subcutaneously) of either BIAsp 30 or NPH-insulin (Insulatard®). Both NPH-insulin and BIAsp 30 were administered

immediately before breakfast and dinner (usually NPH-insulin in this type of insulin regimen is administered 30 minutes before the meals). Insulin experienced patients received their usual pre-trial dose of NPH-insulin or a corresponding dose of BIAsp 30. Insulin naïve patients were initially treated with a starting dose of 8 to 16 IU per day. For both types of patients, insulin doses were adjusted according to blood glucose measurements in accordance with standard diabetes treatment guidelines.

Study population: Male and female Type 2 DM patients (as defined by WHO criteria) aged 18 years or more with a BMI ≤35 kg/m^2 and HbA1c value ≤11.0%. Both insulin naïve patients and patients treated with NPH-insulin (monotherapy or combination with oral hypoglycaemic agents (OHA)) were included.

Study objectives

Primary objective: The primary objective of the trials was to compare the glycaemic control of BIAsp 30 with that of human NPH-insulin patients with type diabetes.

Secondary objectives: Secondary objectives included comparison of safety of BIAsp 30 with that human NPH insulin.

Endpoints

Primary endpoint: The primary efficacy endpoint was HbA1c after 4, 8, 12 and 16 weeks of treatment.

Secondary endpoints: Secondary endpoints included last valid assessment of HbA_{1c}, 8-point glucose profiles after 1, 2, 4, 8, 12 and 16 weeks of treatment, total daily dose of biphasic insulin.

Statistical methods: Sample size calculations were based on a requirement of a power of 80% to detect a difference of 0.3 percentage points in HbA1c levels. The efficacy analysis was based on the intention-to-treat (ITT) population. Supplementary analysis was performed with the per-protocol (PP) population. A repeated measures ANOVA was used to analyse the primary efficacy variable. Hypoglycaemic episodes were analysed using a log-linear Poisson regression model.

Results

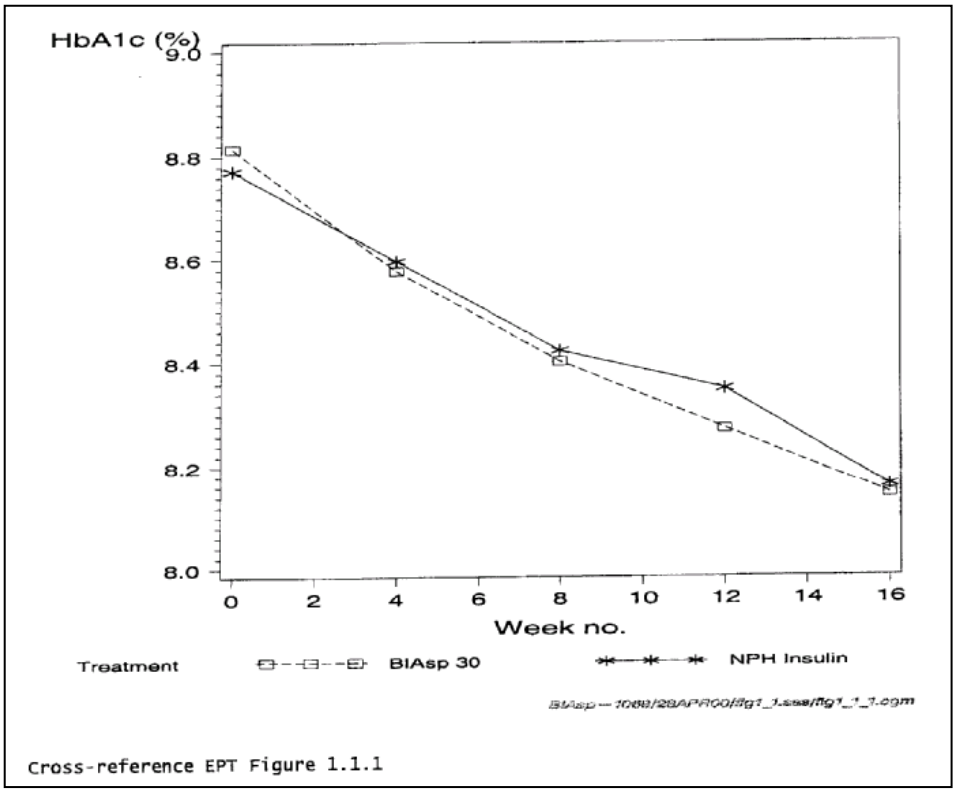
Subject disposition: A total of 485 were screened. Out of these 80 patients were screening failures. 405 patients were randomised. 403 actually received study medication and 392 patients completed the trial. Withdrawals were equally distributed aiming the two treatment groups.

Demographic and baseline characteristics: The two treatment groups were well-balanced as regards demographic parameters and baseline disease characteristics. At inclusion the study population consisted of Type 2 DM patients with an average disease duration of approximately 10 years. Approximately 40% were insulin naïve. Baseline HbA_{1c} levels were approximately 8.8%. Of the insulin naïve patients, the vast majority were previously on OHA. Only very few patients were truly treatment naïve.

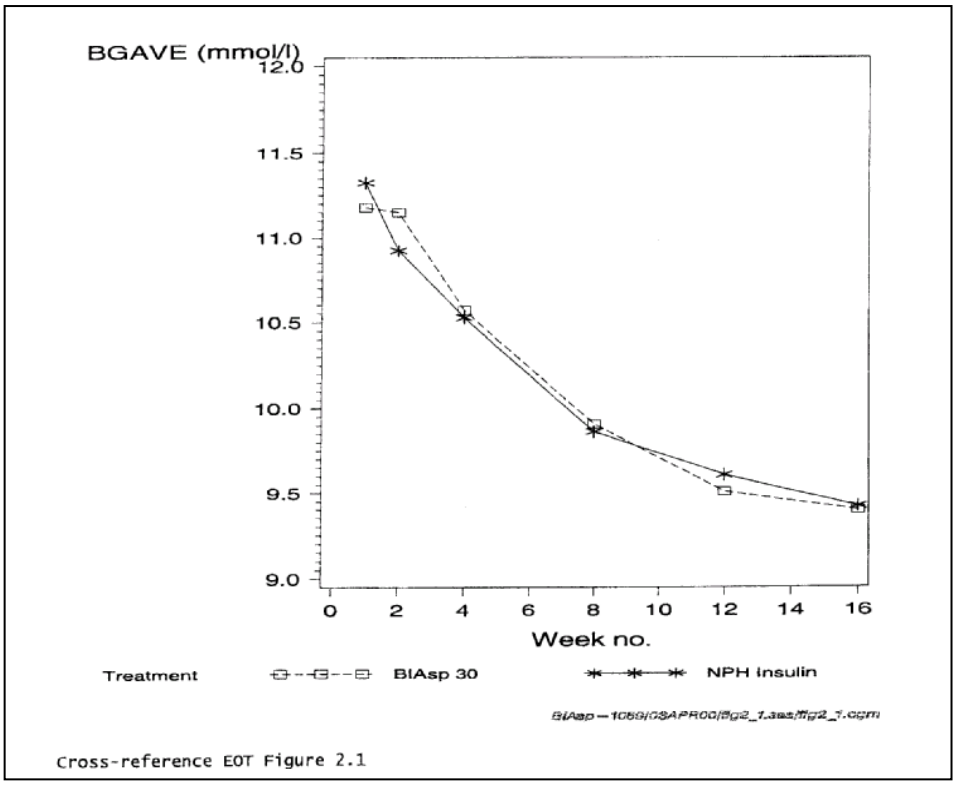
In both treatment groups the total daily insulin dose increased during the study, more so in the BIAsp 30 than in the NPH group.

Primary endpoint: At 16 weeks HbA_{1c} levels had decreased to approximately 8.2% in both treatment groups. There was no significant difference between treatments. The results were similar for both the ITT and the PP analyses. In both treatment groups, HbA_{1c} exhibited a continuous fall during the 16 weeks of treatment without reaching a stable plateau. An exploratory ANOVA interaction analysis of the effect of pre-treatment were performed. As to be expected, patients previously treated with a combination of NPH-insulin and OHA responded less favourable than patients previously on NPH-insulin monotherapy or OHA monotherapy. There were no differences between treatments.

Secondary endpoints: Average blood glucose levels were approximately 11 mmol/l at study entry. In



both treatment groups there was a continuous decrease in average blood glucose levels during the 16 weeks of treatment. At 16 weeks of treatment average blood glucose levels were approximately 9.5 mmol/l in both treatment groups. There was no significant difference between treatments.



It is noted that prandial blood glucose control at breakfast and dinner was superior with BIAsp 30 compared to NPH-insulin. On the other hand, blood glucose levels at lunch time and after over-night fast were statistically significantly higher with BIAsp 30 than with NPH-insulin.

Study INS/UK/002/UK

This was an open, randomised, cross-over study to compare twice daily intermediate acting insulin (Human Insulatard®) and once daily long acting insulin (human Ultratard) in non-insulin dependent diabetic subjects

Study design and study duration: This was an open, randomised, multi-centre, cross-over study. There were two study periods of 6 months thus, total study duration was 1 year.

Study medication: Following a run-in period of 8 weeks where patients continued their oral hypoglycaemic therapy, they were randomised to treatment with Insulatard® or Ultratard for a period of 6 month. Starting dose was for both treatments 0.3 IU/kg/d (and subsequently adjusted to achieve an FBG of 4-7 mmol/l), divided equally between a morning and an evening dose as regards Insulatard®, or administered as a single evening dose as regards Ultratard. After 6 months of treatment patients were switched to the other insulin therapy.

Study population: A BMI <35kg/m^2 and an age between 30 (40?[1]: [1] Different statements on the lower age limit are made) and 80 were required, too, for inclusion. Patients with any insulin therapy 6 months before enrollment, patients with severe renal or hepatic failure or cardiac disease as assessed by the physician and patients with rapidly progressive retinopathy could not be included.

Study objectives:

Primary objective: The primary objective was to assess the safety of twice daily human Insulatard® compared to once daily human Ultratard in terms of the number of hypooglycaemic episodes experienced by each patient.

Secondary objectives: Secondary objectives included the metabolic control. Patients with Type 2 DM being unsatisfactorily controlled (FBG ≥8.5 mmol) by the maximum dose of an oral hypoglycaemic agent could be enrolled.

Endpoints:

Primary endpoint: The primary endpoint was the total number of hypoglycaemic reactions in each treatment period.

Secondary endpoints: Secondary efficacy endpoints were total insulin dose, HbA_{1c}, blood glucose 7- and 4-point profile, weight, cholesterol, HDL, LDL, diabetes quality of life questionnaire, triglycerides, fasting insulin, fasting C-peptide, and overall treatment satisfaction score.

Statistical methods: A sample size of 80 patients was calculated to detect a true treatment difference of 25% in the number of hypoglycaemic episodes, with a power of 80% assuming that the lower incidence of hypoglycaemic episodes was 40%.

Results:

Subject disposition: A total of 73 patients were randomised and received study medication. Of these, 68 patients provided some follow-up data and could be in the safety analysis of hypoglycaemic reactions. Sixty (60) patients completed the study and were included in the efficacy analysis. The reasons for withdrawal in 13 patients were AEs in 2 patients (unlikely related to study medication), in

effective therapy in 6 patients (all were treated with Ultratard at the time), the remaining withdraw for other reasons.

A total of 33 patients (2 withdraw after randomisation) were treated in the sequence Ultratard®-Insulatard®, and 38 were treated in the sequence Insulatard®-Ultratard®, 28 from the sequence U-I. and 32 from the sequence I-U. completed the study.

Primary endpoint:

Insulin doses increased with time irrespective the treatment sequence; overall, the mean Insulatard® dose was in mean 4.9 IU greater than the Ultratard® dose at the end of the treatment periods.

Data on HbA_{1c} are available only for 26 patients from the treatment sequence U-I. and 32 patients from the treatment sequence I-U. Decreases in HbA_{1c} were observed for both treatment sequences. There was an estimated treatment difference of 0.72% in favour of Insulatard® which was statistically significant. Blood glucose control generally was slightly more favourable for Insulatard®.

No analyses were conducted in special populations. The 3 Phase III trials, only included patients ≥18 years thus, there is no paediatric patients included in these studies.

2.6.6. Discussion on clinical efficacy

The treatment of diabetes mellitus (DM) with insulin has been established for many decades. It is a life-saving treatment for patients with Type 1 DM and is required by many patients with Type 2 DM. It is generally accepted that the so-called basal-bolus insulin regime (one or two injections of NPH insulin covering basal insulin requirements in combination with three injections of fast-acting insulin to cover meal-related insulin requirements) generally yields the best glycaemic control in DM.

Insulatard® has been approved for many years initially through the national and later the decentralised procedure. The application is supported by a total of 4 clinical studies in patients with Type I (Trial NN304-1038 and the supportive Trial NN304/DCD/006/D) and Type II DM (Trial Bi-Asp-1069 and Trial INS/UK/002/UK).

Study NN304-1038 was conducted in patients with Type I DM. Overall, the study methodology as a multi-centre, randomised cross-over trial was considered acceptable. The trial was not blinded as this would have meant a double-dummy design with many injections for the subjects. The short duration was also acceptable as the endpoints ($AUC_{glu,23-8}$ and 24-hour serum glucose concentration–time curves do not rely on long-term monitoring (in contrast to e.g. HbA_{1c}). Thus, also the chosen endpoints are considered relevant and acceptable. In this trial NPH insulin was tested against a not authorised long-acting insulin analogue. The trial confirmed the glucose profile obtained by the basal/bolus treatment with NPH insulin given once daily to cover the basal insulin requirements and HI given to the meals. The daily dose is in accordance with the dose recommendations in the SmPC.

Study NN304/DCD/006/D was conducted in patients with Type I DM. The objective of this trial was to gain experience with NN304 in order to find out how to transfer patients on a basal/bolus regimen from NPH insulin once or twice daily to NN304 once daily. Thus, the study is considered supportive. The study results confirm the serum glucose profile of NPH insulin which was comparably shaped as the glucose profile in trial NN304-1038.

Study Bi-Asp-1069 was conducted in patients with Type II DM. Overall, the study methodology as a multi-national, randomised, double-blinded, active-controlled trial was considered acceptable. The duration of 16 weeks was also acceptable as the primary endpoint (HbA1c) is dependent on blood-glucose the previous 12 weeks. The objectives and the primary endpoint is endorsed. The secondary endpoint (8-point glucose profiles at pre-decided time-points during the study) is supporting the

primary endpoint. The primary and secondary endpoints are partly interrelated, however, also relevant for the efficacy of the product and both endpoints are validated endpoints, widely used in clinical trials. A total of 392 patients evenly distributed (also with regard to demographics and baseline characteristics) between the two treatment arms completed the study. Baseline HbA_{1c} was approximately 8.8% indicating that on average, the included patients were mildly dysregulated. In accordance with this observation, the total daily insulin dose increased during the study period. Based on these data, it was expected that HbA_{1c} would decrease during the study period; which was also the observation. At Week 16, mean HbA_{1c} was decreased to 8.2% in both treatment groups thus, no difference between the treatments. No plateau for the HbA1c was observed; this is most likely due to the increasing insulin dose and the short study period/timepoints for measuring HbA_{1c} – taking into account that HbA_{1c} is dependent on blood-glucose the previous 12 weeks. In other words, the duration of the study was too short to fully evaluate the potential benefits of the treatment. Also, the average daily blood glucose level decreased during the study period; from approximately 11 mmol/l to approximately 9.5 mmol/l. This is in accordance with the decrease in HbA1c as these parameters are inter-dependent (as previously mentioned).

Study INS/UK/002/UK was a multi-centre, randomised cross-over trial conducted in patients with Type II DM. The primary endpoint was hypoglycaemic episodes, thus reflecting the safety of Insulatard®. The efficacy was reflected in the secondary endpoint being HbA_{1c}. Despite a sample size of 80 patients were calculated, only 73 patients were randomised and only 68 patients were included in the safety population and 60 patients were included in the efficacy analysis. This severely compromises any firm conclusion based on this study which is therefore considered supportive. It is nevertheless reassuring that a decrease in HbA_{1c} was observed in both treatment sequences with a between-treatment difference of 0.72% favouring Insulatard®. While the difference is hardly clinically relevant and only few patients were included the results from the present study support the results observed in the previous study; namely that treatment with Insulatard® is efficacious and safe.

Upon request, the MAH presented data from six clinical studies where Insulatard® was used in the basal/bolus treatment of paediatric and adolescent patients aged 2-18 years. Study periods were 12-52 weeks and the treatment were compared to other insulin-based therapies as placebo-controlled studies would be unethical. Overall, treatment with Insulatard® was shown to be efficacious. Individual dose titration resulted in appropriate decrease in HbA_{1c}, a validated and acceptable biomarker of effect in blood glucose levels. Changes in HbA_{1c} were most often non-inferior with the comparator.

Taken together, the MAH has sufficiently documented the efficacy of Insulatard® used among children and adolescent <18 years.

Altogether, the present data indicates that both in Type I DM and Type II DM patients, acceptable glycaemic control can be obtained by the administration of Insulatard® either in a twice daily regimen or in a basal-bolus regimen. Both in paediatric and adult patients with Type I DM and in patients with Type II DM, treatment with Insulatard® resulted in a decrease in HbA_{1c} with individually adjusted doses of Insulatard® according to the SmPC.

2.6.7. Conclusions on the clinical efficacy

Both in paediatric and adult patients with Type I DM and in patients with Type II DM, treatment with individually adjusted doses of Insulatard® decreases blood glucose and HbA_{1c}. The data on efficacy are acceptable.

2.6.8. Clinical safety

Information on the safety of BHI is based on three different sources:

- Clinical trials;
- PSUR for the period 1 March 1993 to 31 August 1998 for all recombinant human insulin products marketed by Novo Nordisk including Insulatard®;
- PSUR for the period 1 September 1998 to 30 June 2000 for long-acting biosynthetic human insulin, i.e. Insulatard®, Monotard® and Ultratard®.

2.6.8.1. Patient exposure

Safety data is based on data from approximately 3,000 patients who received insulin in clinical trials. Further, post-marketing experience includes data based on the sales figures and assuming an average of 42 IU insulin per diabetic patient per day, an estimated total of 21 million person years of exposure result, representing at least 4 million individual patients.

2.6.8.2. Adverse events

Across the studies, a total of 63 patients reported 208 AEs while receiving Ultratard® compared to 51 patients reporting 162 AEs while receiving Insulatard®.

Adverse events incidence: 36% and 38% of patients in BIAsp and NPH-insulin groups, respectively, reported one or more adverse events. Most of the adverse events were considered unlikely to be related to treatment. Four patients in each treatment group experienced adverse events with a possible or probable relation to trial medication. The majority of adverse events were mild to moderate in severity. The most frequently reported adverse event in both treatment groups were headache and influenza like symptoms.

Hypoglycaemic episodes:

Across the studies, a total of 220 hypoglycaemic reactions were reported on Ultratard® and a total number of 171 on Insulatard®. There were more severe hypoglycaemic reactions (grade III and IV, i.e. requiring 3rd party help) for Ultratard® (14) than for Insulatard® (1). Overall, there were few major hypoglycaemic episodes in both treatment groups. Numerically, there were more major episodes with BIAsp 30 than with NPH-insulin. However, no conclusion can be drawn due to the small number of episodes and subjects involved. Thirty-eight and 34% of subjects in BIAsp 30 and NPH-insulin groups respectively experienced minor hypoglycaemic episodes.

In Study NN304-1038 (Type 1 DM patients) it was concluded that during treatment with NPH insulin 51 subjects experienced 556 minor hypoglycaemic episodes and 7 subjects experienced 11 major hypoglycaemic episodes. Nineteen AEs were experienced by 15 patients in the NPH treatment periods, 9 of these being respiratory AEs. There occurred no SAEs with NPH treatment. No change was observed in the level of antibodies against human insulin.

In Study INS/UK/002/UK (Type 2 DM patients) it was concluded that a higher number of hypoglycaemic reactions while receiving Insulatard® was reported by 20 patients, while a higher number of hypoglycaemic reactions while receiving Ultratard® was reported by 34 patients. This difference was, however, not statistically significant.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

In the pivotal trial Study Bi-Asp-1069 four subjects reported 5 serious adverse events on BIAsp 30 compared to 10 subjects with 10 serious adverse events on NPH-insulin.

Deaths

No deaths were reported during the pivotal trial Study Bi-Asp-1069.

2.6.8.4. Safety in special populations

No data were presented by the Applicant. The 3 Phase III trials only included patients ≥18 years. In the initially presented data, there were no data of use of Insulatard® in the paediatric population (<18 years), however, this was later presented by the MAH. Safety data from six clinical studies where Insulatard® was used in the basal/bolus treatment of paediatric and adolescent patients aged 2-18 years showed that the safety profile of Insulatard® was comparable with the comparator. In all studies, the most common AEs were reported to be respiratory tract infections, gastrointestinal infections and headache, thus conditions commonly reported in children and adolescents but not expected to be related to treatment. Treatment-related AEs were most often hypoglycaemia; a known AE to insulin treatment. In all six studies, the majority of hypoglycaemic events were mild and only few were considered serious. In studies reporting on nocturnal hypoglycaemic episodes, these were overall few. Other treatment-related AEs included administration site reactions. These are known AEs to insulin treatment which is administered subcutaneously. There are no reports on administration site reactions being more commonly reported in association with Insulatard®.

The post-marketing data presented by the MAH confirm the safety data from the clinical studies. The most commonly reported AEs are within the SOCs 'Metabolism and nutrition disorders', 'General disorders and administration site conditions' and 'Injury, poisoning and procedural complication'. The most commonly reported PTs were 'Blood glucose increased', 'Hypoglycaemia', 'Hyperglycaemia' and 'Drug ineffective'. Whereas the overall AEs picture based on SOCs were rather consistent with the picture observed among adults, the frequency of 'Blood glucose increased', 'Hyperglycaemia', 'Drug ineffective' and to a lesser extent 'Hypoglycaemia' were more commonly reported in paediatric patients. This is most likely due to the fact that children (and adolescents) have an overall less regular life (both with regard to physical activity and to meals); factors known to affect the blood glucose levels. Thus, these differences compared to the adult population are not expected to be related to the product and does not change the positive Benefit-risk of the product also for the paediatric (and adolescent) population.

2.6.8.5. Immunological events

In Study NN304-1038 (Type 1 DM patients) no change was observed in the level of antibodies against human insulin.

Overall, immunogenicity has been a well-characterised risk for more than a decade. Several studies have investigated the risk of developing antibodies to human insulin during treatment with insulin products including Insulatard®. Studies have shown that only few patients develop antibodies to human insulin during treatment with Insulatard® and only few cases have been reported within the last 5 years. A decreasing reporting rate observed within the last 5 years may (partly) be due to a lower reporting rate thus an underestimation of the frequency, which is most likely stable over the years. Taken together, the risk of immunological events is considered well-described, well-known and overall low. No additional information is necessary.

2.6.8.6. Discontinuation due to adverse events

One subject in the NPH-insulin group was withdrawn due to allergy to protamine. Two subjects (one in each group) were withdrawn due to myocardial infarction, in both cases relation to trial medication was considered unlikely.

2.6.8.7. Post marketing experience

PSUR for the period 1 September 1998 to 30 June 2000

No regulatory or manufacturer actions have been taken for safety reasons.

Patient exposure

Clinical trials: an estimated 3,000 patients have received long-acting BHI.

Market experience: Based on the sales figures and assuming an average of 42 IU insulin per diabetic patient per day on a whole year basis, an estimated total of 3.7 million person years of exposure result for this review period, representing at least 2 million individual patients.

Adverse events

A total of 942 AE reports, representing 1041 AEs, are included in this PSUR, 99 of these being SAEs.

The most common AEs were hyper- and hypoglycaemia, injection site reaction and pain, therapeutic response decreased, allergic reaction.

A total of 27 SAE reports were classified as serious unlisted and case reports of these cases are included in the PSUR. Among these were first reports in the Company's safety database on optic atrophy, on limb malformation in a new-born baby (born without limbs and with cardiac problems, subsequently dying) and on thrombocytaemia.

From Japan, 22 reports, 11 of these being serious (no case reports are provided) on impaired liver function were received by the Company. No reports on impaired liver function were received from other countries. It is known from literature that live enzymes may rise, especially in patients with NIDDM, and that they are associated with overweight. According to evidence from some studies liver enzyme increases are related to NIDDM/ intake of oral anti-diabetic agents but not to insulin.

Furthermore, many of the reports concerned semisynthetic, not genetically engineered insulin and last, the hypothesis of an idiosyncratic reaction is abandoned as liver enzymes increased immediately, no other allergy signs were observed and eosinophile granulocytes were not found in biopsies.

Taken together, the post-marketing safety data support the findings from the clinical studies.

2.6.9. Discussion on clinical safety

The treatment of diabetes mellitus with insulin has been established for many decades. It is a life-saving treatment for patients with Type 1 DM and is required by many patients with Type 2 DM. Overall, the present data indicates that both in Type I DM and Type 2 DM patients, treatment with Insulatard® either in a twice daily regimen or in a basal-bolus regimen is safe. Only few patients experienced adverse events. The most obvious and potentially serious adverse reaction is hypoglycaemia. This is, due to the nature of the diseases, most commonly observed in patients with Type 1 DM. Other common adverse reactions are expected to be related to injection site reactions.

Data from six clinical studies where Insulatard® was used in the basal/bolus treatment of paediatric and adolescent patients aged 2-18 years showed that treatment with Insulatard® was comparable with

the Comparator. In all studies, the most common AEs were reported to be respiratory tract infections, gastrointestinal infections and headache, thus conditions commonly reported in children and adolescents but not expected to be related to treatment. Treatment-related AEs were most often hypoglycaemia; a known AE to insulin treatment. In all six studies, the majority of hypoglycaemic events were mild and only few were considered serious. In studies reporting on nocturnal hypoglycaemic episodes, these were overall few. Other treatment-related AEs included administration site reactions. These are known AEs to insulin treatment which is administered subcutaneously. The post-marketing data presented by the MAH confirm the safety data from the clinical studies. The most commonly reported AEs are within the SOCs 'Metabolism and nutrition disorders', 'General disorders and administration site conditions' and 'Injury, poisoning and procedural complication'. The most commonly reported PTs were 'Blood glucose increased', 'Hypoglycaemia', 'Hyperglycaemia' and 'Drug ineffective'. Whereas the overall AEs picture based on SOCs were rather consistent with the picture observed among adults, the frequency of 'Blood glucose increased', 'Hyperglycaemia', 'Drug ineffective' and to a lesser extend 'Hypoglycaemia' were more commonly reported in paediatric patients. This is most likely due to the fact that children (and adolescents) have an overall less regular life (both with regard to physical activity and to meals); factors known to affect the blood glucose levels. Thus, these differences compared to adult population are not expected to be related to the product and does not change the positive Benefit-risk of the product also for the paediatric (and adolescent) population. Overall, the adverse event profile of Insulatard® is comparable across ages groups (children, adolescents and adults).

With regard to immunogenicity, this has been well-characterised for more than a decade and several studies have investigated the risk of developing antibodies to human insulin during treatment with insulin products including Insulatard®. Studies have shown that only few patients develop antibodies to human insulin during treatment with Insulatard® and only a few cases have been reported within the last 5 years. Overall, the risk is considered well-described, well-known and overall low.

There is extensive post-marketing data although the first PSUR also included safety data from other insulins than Insulatard®. Nevertheless, at the time of the initial MAA via the centralised procedure, post-marketing data included data from more than 5 million individual patients. Overall, approximately 10% of the reported adverse events were serious, however, it is expected that serious adverse events are reported more often than well-known mild adverse events, which is also according to at least some national recommendations for reporting of adverse events. Thus, the selection bias should be taken into account and limits the generalisation/extrapolation of the adverse event profile. Nevertheless, post-marketing data confirm that the majority of adverse events are non-serious and related to injection site reactions (e.g. pain and redness), decreased response and hypoglycaemia. In the PSUR from 1 September 1998 to 30 June 2000, new cases of increase in liver enzymes were reported. Of note, a rise in lever enzymes is not abnormal in patients with DM, especially patients with Type 2 DM, and is correlated to fatty liver. Thus, post-marketing safety data support the findings from the clinical studies.

2.6.10. Conclusions on the clinical safety

Sufficient clinical and post-marketing safety data in paediatric and adult population has been submitted. Both in paediatric and adult patients with Type 1 DM and Type 2 DM, treatment with individually adjusted doses of Insulatard® can be considered safe.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.7.3. Risk minimisation measures

None

2.7.4. Conclusion

The CHMP considers the risk management plan version 3.1 acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

A User testing of the Package Leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The purpose of this application (article 58) is to propose an optional storage condition before use (24 months at 2-8°C followed by 4 weeks below 30°C) for specific non-EU countries in warmer climatic zones with limited access to refrigeration. The target indication applied for by the Applicant is for the treatment of diabetes mellitus of both children, adolescent and adult patients. The indication applied for considers both Type 1 and Type 2 diabetes mellitus.

Diabetes mellitus is the most common endocrine disease characterised by hyperglycaemia in the pre- and post-prandial state resulting from defects in insulin secretion, insulin action or both.

Acute, life-threatening consequences of diabetes are hypoglycaemia, and hyperglycaemia with ketoacidosis or non-ketotic hyperosmolar syndrome. Long-term complications of diabetes include microvascular disorders such as: retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy causing foot-ulcers and autonomic neuropathy leading to gastrointestinal, genitourinary, and sexual dysfunction.

Insulin is a key hormone in human metabolism. It lowers blood glucose by suppressing hepatic glucose production by inhibiting gluconeogenesis and stimulating liver glycogen synthase, and by stimulating peripheral glucose uptake in fat and muscle tissue. Furthermore, insulin stimulates lipogenesis by increasing glucose uptake into adipocytes and it inhibits breakdown of triglycerides.

3.1.2. Available therapies and unmet medical need

Treatment with exogenous insulin has been used since 1922. Different formulations exist, which result in different pharmacokinetic properties. Insulatard® is fast-acting, whereas Insulatard® is long-acting and Ultratard is very long-acting. No single standard exists for pattern of administration of insulin and treatment plans vary from physician to physician, for individual patients. Accordingly, insulin requiring diabetic patients can use a variety of different regimens to treat their diabetes. They can either use long- or very long-acting insulin once or twice daily at morning and/or at evening.

Fast-acting insulin can be added to these injections in the morning and the evening to deal with the glucose load in response to the breakfast or evening meal. In an even more intensified regimen fast-acting insulin is given at each main meal and very long- or long-acting insulin are given either at bedtime alone or both at breakfast and bedtime.

Some patients are treated with continuous subcutaneous insulin infusion using an insulin pump where fast acting buffered insulin e.g. Velosulin is administered on a continuous basis with bolus administration at meals.

Adequate control of blood glucose monitored daily and with control of HbA_{1c} every three month is the cornerstone of managing DM. For patients with Type 1 DM, the only available treatment is subcutaneous injections with short- and/or long-acting insulin. Patients with Type 2 DM can be managed with oral antidiabetics, GLP-1 analogues but a substantial proportion will also need supplemental treatment with daily subcutaneous insulin injections.

3.1.3. Main clinical studies

The clinical documentation in the application for the MAA via the centralised procedure was chosen from 5 sources of clinical studies and data:

- Recent performed studies where Insulatard® has been used as comparator in clinical trials that are performed to demonstrate efficacy and safety for substances under development i.e. Insulin Detemir and Biphasic Insulin Aspart.
    - NN304-1038: Multi-centre, open, randomised, crossover trial to compare the blood glucose lowering effect of NN304 with NPH insulin in type 1 diabetic subjects.
    - NN304/DCD/006/D: A multicentre, uncontrolled open, titration study of the new long/intermediate acting insulin analogue NN304 in a basal/bolus regimen in type 1 diabetic patients.
    - Bi-Asp-1069: A multinational, randomised, controlled double-blind, parallel group efficacy and safety comparison of twice daily biphasic insulin aspart 30 or human NPH insulin in subjects with type 2 diabetes.
    - INS/UK/002/UK: An open, randomised, cross-over study to compare twice daily intermediate acting insulin (Human Insulatard®) and once daily long acting insulin (human Ultratard) in non-insulin dependent diabetic subjects.

In support of the initial MAA for Insulatard®, the MAH submitted a total of two studies considered as pivotal studies as well as two supportive studies. Two studies (also one supportive study) were conducted in patients with Type 1 DM and two studies were conducted in patients with Type 2 DM.

The treatment of DM with insulin has been established for many decades. It is a life-saving treatment for patients with Type 1 DM and is required by many patients with Type 2 DM. It is generally accepted that the so-called basal-bolus insulin regime (one or two injections of NPH insulin covering basal insulin requirements in combination with three injections of fast-acting insulin to cover meal-related insulin requirements) generally yields the best glycaemic control in DM.

3.2. Favourable effects

The present data demonstrates that both in Type 1 DM and Type 2 DM patients, acceptable glycaemic control can be obtained by the administration of Insulatard® either in a twice daily regimen or in a basal-bolus regimen. Both in patients with Type 1 DM and in patients with Type 2 DM, treatment with Insulatard® resulted in a decrease in HbA1c with individually adjusted doses of Insulatard®.

3.3. Uncertainties and limitations about favourable effects

None

3.4. Unfavourable effects

Overall, the most commonly reported adverse events related to treatment with Insulatard® was hypoglycaemia. In the clinical studies, hypoglycaemic episodes were reported in a comparable proportion among the Insulatard®-treated population and the Ultratard (comparator)-treated population and overall, more hypoclycaemic episodes were reported among patients treated with biphasic insulin aspart 30. Among the clinical trials, only one patient treated with Insulatard® reported severe hypoglycaemic reactions (grade III and IV) which is reassuring. Due to the pathogenesis of the

diseases, more hypoglycaemic episodes are expected among the Type 1 DM patients compared to the Type 2 DM patients. Other reported adverse events are related to injection site reactions including redness, swelling and itching. These are transient and often mild in severity.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The cornerstone in treatment of diabetes, is adequate control of blood glucose monitored daily, and with control of HbA_{1c} every three month. This justifies that the most important favourable effect observed was for the endpoint, HbA_{1c} up to 16 weeks after treatment, where Insulatard® reached glycaemic control, indicating that Insulatard® is very effective in lowering blood glucose in both Type 1 and Type 2 DM patients. The evidence of efficacy provided in the trials, was considered convincing.

The adverse event profile of Insulatard® is well-known. Most adverse events are related to the pharmacodynamic effect of the product and relates to hypo- or hyper-glycaemia. These are most often manageable.

Sufficient data to support the use of Insulatard® in the treatment of paediatric, adolescent and adult patients with diabetes mellitus have been provided.

3.6.2. Balance of benefits and risks

The observed metabolic control that was achieved in all trials, is considered clinically relevant, as the glycaemic control was reached through evaluation of HbA_{1c}. The evidence provided is considered convincing and considering all favourable and unfavourable effects the benefit-risk balance is positive.

3.6.3. Additional considerations on the benefit-risk balance

In this application (art. 58), the Applicant proposed an optional storage time before use (4 weeks below 30°C) to meet the request from humanitarian actors of an alternative use of Insulatard® under challenging temperature conditions in relevant non-EU countries with limited access to refrigeration.

The evaluation from the Applicant supports adequate quality of the drug product at the end of in-use period after storage at the proposed optional condition. However, one recommendation for an in-use stability study with batches stored at the optional storage condition before use is raised (and acknowledged by the applicant) in order to confirm the quality of Insulatard® after a combined storage period at the proposed optional storage condition and in-use condition.

The proposed update to the storage conditions to facilitate use under challenging temperature conditions in settings with limited access to refrigeration has been evaluated in relation to the existing benefit-risk profile of Insulatard®. The storage conditions are described in the proposed product information. Furthermore, instructions in the professional and patient sections detail how the product carton should be used to track the date when the product is taken out of refrigeration. The aim of this instruction is to mitigate the risk of incorrect storage.

It has been concluded that no additional pharmacovigilance activities relating to the proposed storage conditions are deemed necessary. Insulatard® has been marketed in the countries in scope for this application (low to middle income non-EU countries) for more than 30 years and the Applicant has already a solid Pharmacovigilance System in place that has been adapted to the patients and Health Authorities in the countries in scope.

3.7. Conclusions

The overall benefit/risk balance of Insulatard® is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP adopted by consensus a scientific opinion as the benefit-risk balance of Insulatard® in the treatment of diabetes mellitus is favourable. The scientific opinion is subject to the attached product information and the following condition(s).

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the scientific opinion

- **Periodic Safety Update Reports**

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Scientific opinion Holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application 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.