22 April 2022
EMA/254999/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Actrapid

International non-proprietary name: insulin human

Procedure No. EMEA/H/W/005779/0000

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 Actrapid®.

The eligibility by the World Health Organisation was agreed-upon on 10 December 2020.

Actrapid® 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 Actrapid® on	22 April 2022

2. Scientific discussion

2.1. Problem statement

This is an application for Actrapid® (insulin human) submitted under article 58 of regulation (EC) No 726/2004 (H0005779). Eligibility for submission of this application under Article 58 has been confirmed by EMA and WHO on 10 December 2020. The therapeutic indication for Actrapid® is treatment of diabetes mellitus. Actrapid® is currently approved in the EU with product number EMEA/H/C/000424. Actrapid® is approved and has been marketed globally for more than 30 years. At present, Actrapid® is approved in 149 countries and launched in 139 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 Actrapid® 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-year 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.

Actrapid® is a genetically engineered fast-acting human insulin which was approved in 1988 and has been widely used (please refer to the figures on patient exposure from post-marketing data below).

The assessment of the clinical pharmacology, efficacy, and safety of Actrapid® is based on previously reported studies comparing Actrapid® and NovoRapid (insulin aspart, a human insulin analogue).

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-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 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

Actrapid® is a genetically engineered fast-acting human insulin which was approved in 1988 and has been widely used (please refer to the figures on patient exposure from post-marketing data below).

The evidence to support the efficacy of Actrapid® is based on previously submitted studies comparing Actrapid® and NovoRapid® (insulin aspart, a human insulin analogue). Three phase III studies comparing Actrapid® with NovoRapid® investigating the efficacy and safety of the products were submitted. In essence these studies are uncontrolled as far as the efficacy of Actrapid® is concerned as NovoRapid® cannot be considered an adequate comparator, as proof of efficacy of NovoRapid® rests on comparisons with Actrapid. However, the lack of controlled trials is considered acceptable as it would be unethical to perform a placebo-controlled study, and as insulin, especially fast acting insulin, is the mainstay in treatment of diabetes one can hardly imagine what should be chosen as active comparator. The 'uncontrolled' data from the NovoRapid® studies are therefore considered sufficient to provide evidence of the long-term efficacy and safety of Actrapid® in line with the three studies (035/EU, 036/USA and 037/USA) which were the studies provided to support the EU approval of Actrapid® in 2002.

The purpose of this application is to get an assessment of a proposed update to the storage conditions for Actrapid® 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 emphasise 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 solution for injection in a vial containing 10 ml insulin human equivalent to 1,000 international units (IU); solution for injection in a cartridge containing 3 ml insulin human equivalent to 300 IU and solution 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, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

The product is available as follows: Actrapid® in a vial (type 1 glass) closed with a disc (bromobutyl/polyisoprene rubber) and a protective tamper-proof plastic cap containing 10 ml of solution; Actrapid® Penfill® in a cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of solution; Actrapid® FlexPen® in a cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) containing 3 ml of solution 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 Actrapid® 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.

Process validation

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

- Validation of the NN729 (current), NN729 (optimised) process, and modified process
- Evaluation of impurity removal by the NN729 (current), NN729 (optimised), 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 optimised) 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 optimisation 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 (optimised) 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 (optimised) and NN729 (current).

Characterisation

Structural characterisation and elucidation of the physico-chemical properties of Insulin Human has been performed. The applicant confirmed the theoretical and expected structure of insulin human active substance produced by the NN729 (current and optimised) 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 optimised 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 Actrapid® formulation is a sterile multidose neutral aqueous solution. This application (art. 58) concerns the 100 IU/ml strength.

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

Since the development of pH-neutral insulin in the early 1960s, which forms the basis for the present Actrapid® formulation, additional development work has been performed including introduction of rDNA human insulin and changes in preservative and isotonic agents leading to the present composition of Actrapid® products which were introduced on the market in the 1980s. The present composition and manufacturing procedure for Actrapid® preparations have been proven satisfactory through several years manufacturing of batches with results of analyses within specification limits. This is supported by various validation and stability studies.

Compatibility of the container components and product is shown to be satisfactory. The primary packaging is as follows: the 10 ml vial is a glass container consisting of a cap with a rubber disc. The glass container is produced from type I Ph.Eur. colourless glass. The cartridges consist of a 3 ml type I Ph.Eur., colourless glass cartridge sealed with a rubber stopper and a rubber plunger. The FlexPen is a multidose pre-filled pen made of a plastic injector device fitted with 3 ml cartridges. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

Actrapid® 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 Actrapid® 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 (Actrapid®) 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 preservative and for dose accuracy (FlexPen® only). Full methodologies have been provided for in-house methods as well as complete justifications 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.

The provided risk evaluation confirms that there is no risk of nitrosamine presence for the Actrapid® 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 Actrapid® 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 Actrapid® of 30 months at 5°C and in-use storage condition of 6 weeks at 30°C for both the Penfill/FlexPen and vial presentations.

In this application (art. 58), Novo Nordisk proposed an optional storage time before use (4 weeks below 30°C) to meet the request from humanitarian actors of an alternative use of Actrapid® under challenging temperature conditions in relevant non-EU countries with limited access to refrigeration. The applicant evaluated this alternative storage period using long-term stability data batches of Actrapid® 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 Actrapid® 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 Actrapid® 10 ml vial, 100 IU/ml and one batch of Actrapid® 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 Actrapid® 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 Actrapid® 10 ml vial, 100 IU/ml and one batch of Actrapid® 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

Actrapid® is a genetically engineered fast-acting human insulin which was approved in 1988 and has been widely used (please refer to the patient exposure from post-marketing data below). Actrapid® is currently approved in the EU (EMEA/H/C/000424) and has been marketed globally for more than 30 years, and at present Actrapid® is approved in 149 countries and launched in 139 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 Actrapid® 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.

Therefore, the non-clinical data originally submitted as part of the initial marketing authorisation application (MAA) for Actrapid® in the EU provide the basis of the non-clinical assessment for this article 58 procedure.

All studies are 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.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The studies summarised are the studies that were provided in order to support the EU approval of Actrapid® in 2002. Insulin HM(ge) is synonymous to Actrapid®.

The pharmacodynamic studies *in vitro* and *in vivo* presented, support the proof-of-concept for the mode of action of Actrapid®. Together with the extensive clinical data obtained from use of Actrapid® over decades, the evidence of pharmacodynamic effects of the product are well known and no new non-clinical studies are required for this application.

2.5.2.2. Secondary pharmacodynamic studies

No studies presented. The lack of any specific secondary pharmacology studies is accepted based on the long-term clinical use of Actrapid®.

2.5.2.3. Safety pharmacology programme

The applicant performed a comprehensive program of safety pharmacology studies to support the initial EU MA for Actrapid® in 2002. No specific hazards were identified. Together with extensive clinical safety data, these studies are considered acceptable for this article 58 procedure.

2.5.2.4. Pharmacodynamic drug interactions

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

2.5.3. Pharmacokinetics

As the majority of the insulin HM(ge) preparation (Actrapid®) is of same composition as the semi-synthetic insulin HM(ss) preparations, no pharmacokinetic studies were conducted in the original preclinical programme. Linearity concerning AUC/dose was confirmed in different relevant species, meaning that there was no drug accumulation.

No studies on absorption, distribution, metabolism and excretion were conducted with insulin HM(ge) and HM(ss). For a biological medicinal product with extensive clinical usage, this is acceptable.

Toxicokinetics studies were conducted during the 'newer' 52 weeks studies 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. C_{max} 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 Actrapid® has extensive clinical PK data that supersedes the need for new non-clinical data.

2.5.4. Toxicology

The toxicology studies submitted with the original application for Actrapid® were quite limited. At that time, the guidelines and requirements for biological products were of another standard than current guidance. However, as the product is marketed and has extensive clinical data to support the safety and efficacy, no new toxicology studies are warranted for this article 58 procedure.

2.5.4.1. Single dose toxicity

In mice and rats at dosages up to 4000 U/kg, no treatment related signs apart from few sporadic hypoglycaemic reactions were seen.

2.5.4.2. Repeat dose toxicity

In a 4-week SC study 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, 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) 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 highest dose. At 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 application, 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 Actrapid® are of course of older date. However, as none of the original studies on genotoxicity raised concern for safety, and the many years of clinical use of insulins has not raised concerns on this area, the original studies are considered sufficient for this article 58 procedure for an already approved product.

2.5.4.4. Carcinogenicity

In the original EU MAA, the basis for the preclinical testing was to confirm that there were no biological difference between the marketed semi-synthetic human insulin HM(ss) and the chemical identical HM(ge) produced by another method. No biological difference was seen in the short-term studies and carcinogenicity of human insulin was not an issue for the risk analysis. However, during the last decades, new insulin analogues have been produced, and the attention has been drawn to the carcinogenic potential of insulin due to its metabolic and weak mitogenic actions. The use of new insulin analogues instead of HM has raised the question of different carcinogen potency of insulin analogues. In connection with the development of insulin aspart, screening studies have been conducted in order to enlighten this issue.

In a 12-month test in the Sprague-Dawley rat there was a dosage-related increase in palpable subcutaneous masses at 30 and 75 U/kg/bid. A statistically significant ($p<0.01$) increased incidence of female animals bearing mammary gland tumours at 75 U/kg/bid were found. The increase was evident in benign/malign combined as well as in malign tumours alone.

Importantly, no evidence of mammary gland hyperplasia or of tumours was seen in the test up to 12 months in the dog. It can reasonably be concluded that particularly under certain experimental conditions insulins may induce mammary tumours in the female Sprague Dawley rat, a sensitive species, strain and sex, probably because of a mitogenic and growth-promoting action via the insulin receptor.

Recently, the human epidemiological literature has been reviewed (Friis and Dideriksen, 1999) for evidence of association between diabetes mellitus 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 has been documented. Therefore, the non-clinical studies from the original application for Actrapid® are considered valid for the current article 58 procedure.

2.5.4.5. Reproductive and developmental toxicity

Reproduction toxicity studies were not conducted for the original application, as insulin is known to have teratogenic potential, and because of the close chemical relationship between Actrapid® and HM(ss).

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.

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

Clinical data from years of use of Actrapid® 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 Actrapid® 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. C_{max} 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 Actrapid® has 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 Actrapid® through decades supersedes the need for non-clinical data.

2.5.4.8. Other toxicity studies

No dedicated studies performed. Actrapid® 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

The applicant submitted and Environmental risk assessment report, consisting of a justification for not performing any ERA studies, as Insulin human is a natural protein, produced by *Saccharomyces cerevisiae* by recombinant DNA technology. This is accepted.

2.5.6. Discussion on non-clinical aspects

Actrapid® is a genetically engineered fast-acting human insulin, which was first approved in 1988 and as a consequence a lot of knowledge is currently available based on the patient exposure from post-marketing data. Actrapid® is currently approved in the EU (EMEA/H/C/000424) and has been marketed globally for more than 30 years, and at present Actrapid® is approved in 149 countries and launched in 139 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 Actrapid® 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.

Therefore, the non-clinical data originally submitted are considered sufficient for this article 58 procedure and no new studies or documentation were provided as part of this Application, which is acceptable.

All studies 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 pharmacodynamic studies *in vitro* and in vivo reflect the studies presented in the original MAA for Actrapid® and support the proof-of-concept for the mode of action. Together with the extensive clinical data obtained from use of Actrapid® over decades, the evidence of pharmacodynamic effects (proof-of-concept) of the product are well known. An extensive safety pharmacology program was performed to support the initial EU MAA for Actrapid®, and these studies are still considered valid, together with the available clinical safety data through years use.

Non-clinical pharmacokinetic data are presented, but superseded by clinical PK data.

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

It could be considered if new or additional studies of genotoxicity should be performed for the current application, as new guidance on this area was implemented with the ICH M7 guideline. The studies supporting the original MA application for Actrapid® are of course of older date. However, as none of the original studies on genotoxicity raised concern 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 application for an already approved product.

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 Actrapid® product which has been marketed since 1988, the non-clinical studies from the original application for Actrapid® are considered valid for the current article 58 procedure.

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, Actrapid® is not expected to pose a risk to the environment.

Considering the above data, Actrapid® is not expected to pose a risk to the environment.

The use of insulins in children, with overwhelming clinical experience of safety and efficacy supersede the need for non-clinical juvenile animal studies.

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 Actrapid® in 2001. The product is identical (no quality changes) to the already approved Actrapid® product. No new non-clinical data has been submitted or discussed by the applicant for this procedure.

Due to the extensive clinical use of Actrapid® and the vast knowledge on the safety and efficacy of insulins that 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

An overview of included studies that evaluate the pharmacokinetic and pharmacodynamic profile of Actrapid® is provided below.

Study 022/UK

A randomised double-blind cross-over trial to compare the plasma insulin profile of a single dose of insulin analogue X14 with that of human Actrapid® in healthy volunteers.

Study 023/D

A two-period double-blind randomised cross-over trial to compare the pharmacodynamic response to a single dose of Insulin analogue X14 with that of Actrapid® HM (ge) in healthy volunteers during a euglycaemic clamp.

Study 026/US

A six-period, double-blind, randomised, cross-over trial to compare the action profile of insulin analogue (X14) in healthy subjects using different injection sites during an euglycaemic clamp, and to compare X14 profiles with profiles of Novolin R.

Study 027/D

A parallel, randomised, double-blind trial to investigate the intra-subject and inter-subject variations in action profiles after injection with Insulin X14 or human soluble insulin during a euglycaemic clamp.

Study 024/UK

A randomised double-blind three-way cross-over trial to compare the effects on postprandial glycaemic excursion of X14 given immediately before a test meal, with human Actrapid® given immediately before or 30 minutes before a test meal in Type I diabetics.

Study 025/UK

A multicentre randomised, double-blind crossover trial to compare the metabolic control obtained with insulin analogue X14, with the metabolic control obtained with human Actrapid®, in type I diabetic patients.

Study 030/DK/N

A randomised two centre double-blind 3-way cross–over trial to compare the effects on post prandial glycaemic excursions of X14 given immediately before a test meal, with Actrapid® given immediately before or 30 minutes before a test meal in insulin treated type 2 diabetic patients.

Study 043/DK

A single centre, randomised, double-blind, cross-over study on the pharmacokinetics of insulin aspart and soluble HI in paediatric type I diabetic subjects.

Study 035/EU

A six-month multicentre, multinational, randomised, parallel, open-labelled, efficacy and safety comparison of insulin aspart (NovoRapid) and Actrapid® as meal-related insulin in a multiple-injection regimen in type I diabetic subjects.

Study 036/US

A six-month multicentre, randomised, parallel, open-label, efficacy and safety comparison of X14 and HI as meal-related insulin in a multiple-injection regimen in subjects with type I diabetes.

Study 037/US

A six-month multicentre, randomised, parallel, open-label, efficacy and safety comparison of X14 and HI as meal-related insulin in a multiple injection regimen in subjects with type 2 diabetes.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

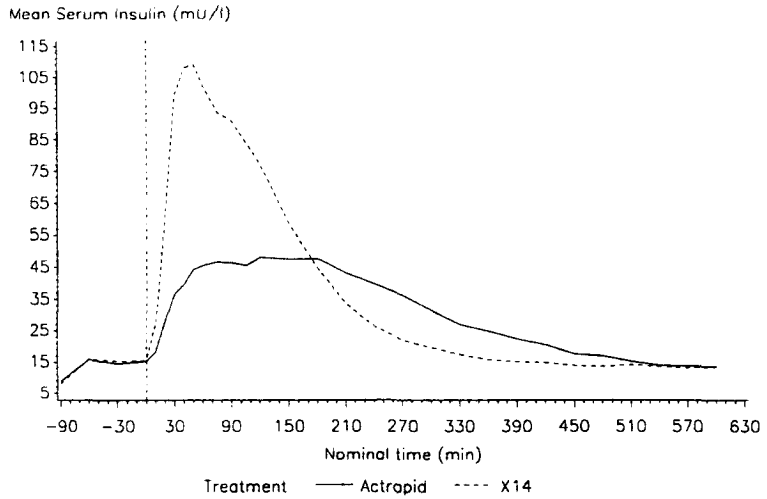
The following table summarises the mean (SD) pharmacokinetics of HI (Actrapid®) in healthy subjects from studies 022/UK, 023/D, and 027/D:

	C_{max} (mU/l)	T_{max} (min)[a]	MRT (min)	AUC (mU/lxh)[b]
022/UK	17.5 (4.3)	120 (15-360)	217 (30.3)	77.8 (13.9)
023/D	55.2 (8.5)	120 (30-270)	238 (21.7)	303 (31.7)
027/UK	46.5 (9.5)	150 (30-420)	240 (25.5)	251 (35)

a. median (range)

b: 0-8h in 022/UK, in the other studies 0-10h

The figure below illustrates the mean insulin profiles in healthy volunteers during euglycaemic clamp (taken from study 023/D):



Study 26/US

The means (SD) for insulin PK parameters (adjusted for endogenous insulin) are displayed in the table below:

	Deltoid	Abdomen	Thigh
AUC (pmol x min/l)	47013 (10469)	47362 (11881)	44171 (5294)
C_{max} (pmol/l)	220 (99)	227 (93)	188 (71)
T_{max} (min)	103 (74)	110 (64)	124 (75)
MRT (min)	198 (44)	186 (43)	198 (48)

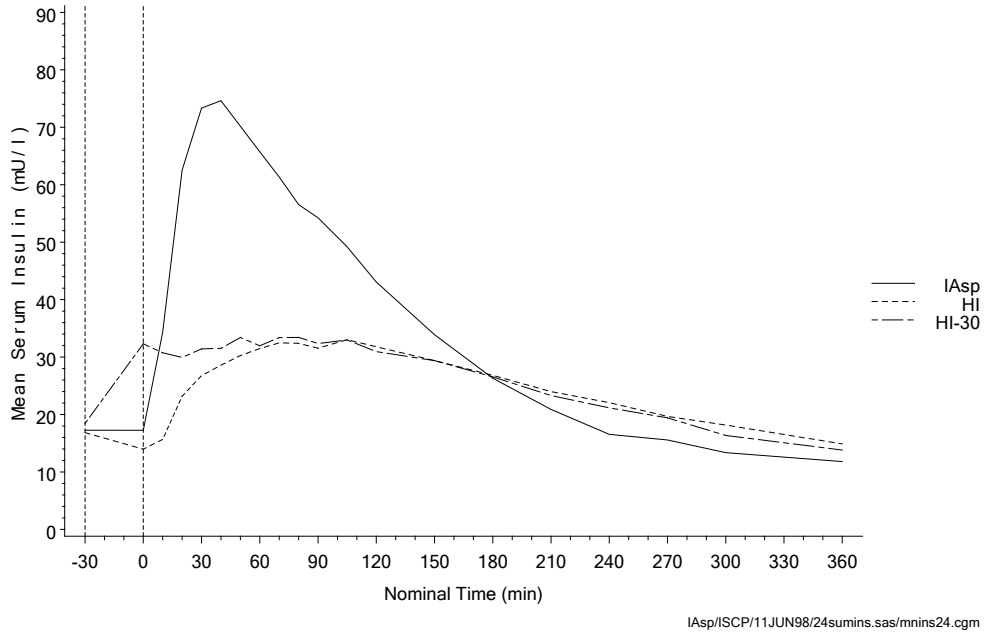
Study 024/UK

22 type 1 diabetic subjects were clamped overnight using an i.v. insulin infusion to obtain pre-dose blood glucose concentrations between 5 and 8 mM. All injections were given s.c. into the anterior abdominal wall. Glucose and insulin (Actrapid®) profiles were followed for a total period of 360 min after the meals. During this period, EXC(BG) (total excursion of blood glucose concentration) was lower after HI given 30 min prior to the meals. C_{max}, glucose was lower when Actrapid® was given 30 min before the meal. AUC_{ins} and C_{max}, insulin were slightly higher when HI was administered 30 min before the meal.

T_{max} insulin was reached in half the time when HI was given 30 minutes before the meal compared to administration immediately before the meal.

It thus appears that administration of HI 30 minutes before a meal is advantageous compared to administration of HI immediately before a meal with respect to postprandial blood glucose control, has a lower maximum blood glucose concentration which is consistent with a higher maximum insulin concentration, the maximum insulin concentration is reached faster.

The insulin profile of Actrapid® given immediately before or 30 minutes before a test meal can be seen in the figure below.



Distribution

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

Elimination

The terminal half-life is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life (t½) is therefore a measure of the absorption rather than of the elimination *per se* of insulin from plasma (insulin in the blood stream has a t½ of a few minutes). Trials have indicated a t½ of about 2-5 hours.

Dose proportionality and time dependencies

Not applicable.

Special populations

No information on pharmacokinetics in subjects with impaired renal function, impaired hepatic function and pharmacokinetics in elderly has been submitted.

From literature it is known that degradation of insulin primarily occurs in the liver and kidney. As insulin administered subcutaneously does not undergo first pass removal by the liver, the kidney has increased importance in removal of insulin and impairment may decrease insulin requirements (Insulin degradation: Progress and potential. Duckworth et al., Endocrine Reviews 19(5): 608-24)

As far as elderly are concerned, it is referred to in the ER that there are no indications from literature that kinetics is different and that elderly rarely are treated with intensified regimens but that treatment is more directed in avoiding hypoglycaemic events and hyperglycaemia.

Children

9 subjects aged 6-12 years and nine subjects aged 13-17 years, were included in trials **-043**. The dose administered s.c. into the abdominal wall immediately before breakfast was 0.15IU/kgbw for both X14 (=Novorapid) and HI (=humanised insulin). Results are shown below.

HI	**6-12 years (n=9)**	**13-17 years (n=9)**	**All**
$C_{max(ins)}$ (mU/l)			
Mean	59	82	70
Median	56	65	58
SD	16	40	32
$AUC_{0-5h\,(ins)}$ (mU/l x h)			
Mean	179	313	246
Median	186	278	201
SD	69	186	153
$T_{max(ins)}$ (min)			
Mean	77	99	88
Median	70	105	75
SD	28	48	40
EXC $_{0-4h\,(glu)}$ (mmol/l x h)			
Mean	25.3	21.3	23.3
Median	22.8	17.4	20.3
SD	14.0	9.5	11.8
EXC $_{0-5h\,(glu)}$ (mmol/l x h)			
Mean	30.8	26.4	28.6
Median	27.6	23.6	26.8
SD	15.5	11.9	13.6
$C_{max\,(glu)}$(mmol/l)			
Mean	22	19	20
Median	21	18	20
SD	5	3	5
$C_{min\,(glu)}$(mmol/l)			
Mean	11	9	10

Median	11	11	11
SD	4	3	4
$T_{max\ (glu)}$ (min)			
Mean	143	108	125
Median	150	105	105
SD	52	55	55
$T_{min(glu)}$ (min)			
Mean	33	77	55
Median	10	10	10
SD	60	109	88
Exploratory analyses			
$AUC_{0-\infty(ins)}$ mU x h/l)			
Mean	275	612	444
Median	259	503	343
SD	139	451	367
$T_{½(ins)}$ (h)			
Mean	3.0	4.0	3.5
Median	2.7	3.5	3.0
SD	1.4	2.4	2.0
MRT_{ins} (min)			
Mean	129	141	135
Median	137	144	141
SD	16	13	38

Pharmacokinetic interaction studies

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

The blood glucose lowering effect of insulin is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

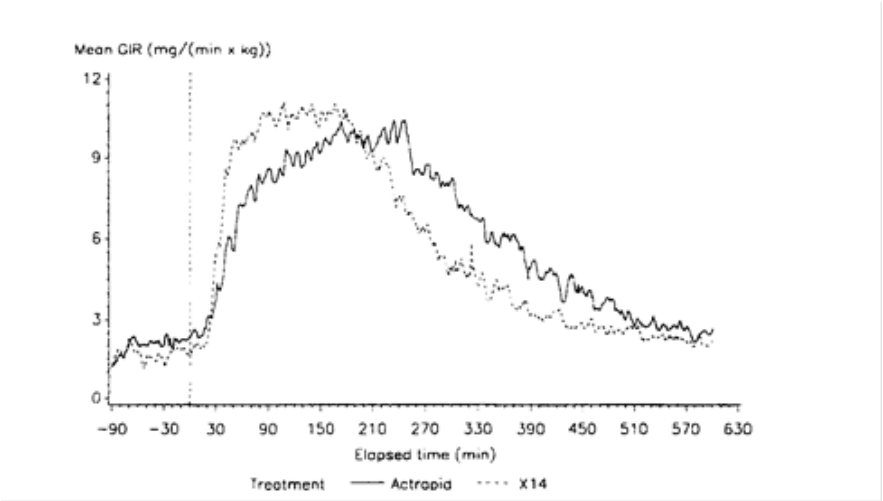
Primary and Secondary pharmacology

Study 023/D:

The primary glucose endpoints had the following results (means(SD)) for Actrapid®:

AUC_{GIR} 3.7 (0.7) g/kg, GIR_{max} 12.1 (2.6) mg/(min x kg), $TGIR_{max}$ 180.8 (56.8) min, $T_{AUC½}$ 235.9 (23.4) min.

The figure below shows the mean GIR profiles:



Study 026/US:

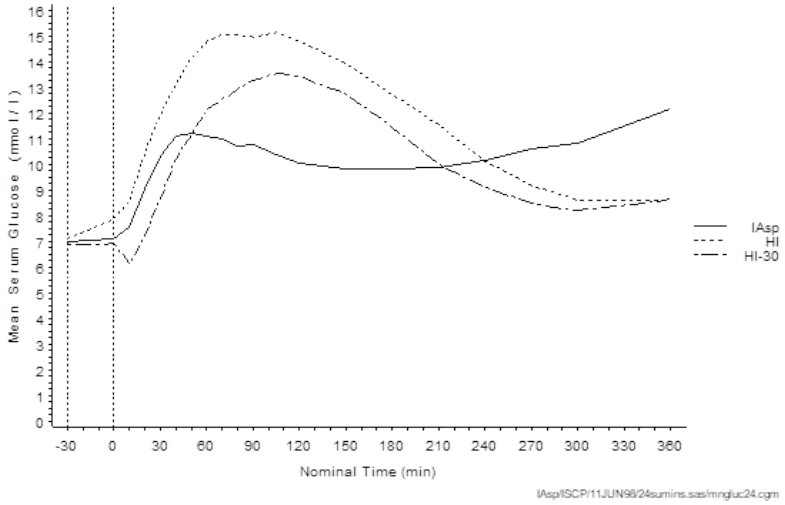
Results of the PD parameters for HI (Actrapid®) (mean (SD)):

GIR (Glucose infusion rate):

	Deltoid	Abdomen	Thigh
AUC (mg)	204519 (56189)	192010 (47896)	205773 (53704)
GIR_{max} (mg/min)	736 (243)	708 (204)	720 (229)
T_{max}(min)	192 (51)	173 (62)	193 (60)
$T_{AUC½}$ (min)	243 (37)	235 (46)	243 (37)

Study 024/UK:

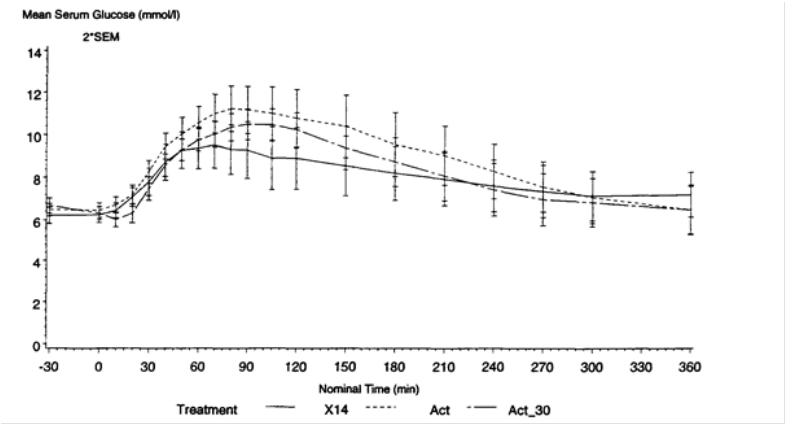
Mean serum Glucose profiles



Study O30:

Twenty-two subjects with type II diabetes were included. Glucose excursions were determined during the period from 0 to 360 minutes after the insulin injections (primary endpoint).

The figure below shows the mean serum glucose profiles for Actrapid® administered immediately before and 30 minutes before a test meal as well as the one for X14.



The blood glucose excursions in study 030/DK/N in type 2 diabetic patients appeared to be lower, as expected, compared to the ones in type I diabetic patients in study 024/UK. In both studies, the injection of HI (Actrapid®) 30 minutes before a meal was more favourable regarding the blood glucose excursions compared to injection immediately before a meal.

2.6.3. Discussion on clinical pharmacology

The assessment is based on previously performed studies that characterise the PK/PD profile for Actrapid®, and the results from these studies was compared to the current EU SmPC for Actrapid® to ensure alignment between literature and current SmPC.

The clinical studies that generated PK/PD results for Actrapid®; studies O22, O23, O26, and O27 were all performed in healthy volunteers. Studies O24 and O25 were performed in patients with type 1 diabetes, and finally study O30 included patients with type 2 diabetes. Study O43, included paediatric

patients with type 1 diabetes. According to the indication, it is considered optimal that the populations presented within the studies, reflect the applied indication, i.e. patients with diabetes mellitus. The studies provided support the indication that is applied for i.e. the current EU indication within section 4.1 of the SmPC 'Treatment of diabetes mellitus'.

Additionally, Actrapid® is administered subcutaneously by injection in the abdominal wall, the thigh, the gluteal region or the deltoid region (in line with section 4.2 of the SmPC). The pharmacokinetic results from the above studies support this posology. Also as regard the special populations, relevant data in children is highlighted in section 5.1 of the SmPC, and both elderly and patients with renal impairment and hepatic impairment are advised to have intensified glucose monitoring and to adjust the insulin dose according to this on an individual basis (SmPC section 4.2). This is also in accordance with the data provided in this application.

The studies were conducted in healthy volunteers, type 1 and type 2 diabetic patients mainly by using the euglycaemic clamp technique and confirm the glucose lowering action of Actrapid®. The studies performed in healthy subjects support the conclusions made in the SmPC on the onset of action, duration of action and the time of the maximum effect. From the studies in diabetic subjects it can be concluded that the administration of Actrapid® 30 minutes before a meal (vs. directly before a meal) is more favourable as regards the total excursions of blood glucose concentrations. All of the provided data support the text in the current SmPC regarding the pharmacodynamic properties of Actrapid®.

2.6.4. Conclusions on clinical pharmacology

Overall the pharmacokinetic and pharmacodynamic results provided in this application support a positive benefit-risk evaluation.

2.6.5. Clinical efficacy

In the clinical documentation in the application from 1987 the expert report was based on a small (13 patients) Phase II study and 5 Phase III studies with a total of 189 patients treated for 1 year in trials comparing insulin HM (ge) and insulin HM (ss) both for 100 U/ml and 40 *U/ml.* Assessment of efficacy was based on mean blood glucose from home monitoring, HbAlc, and daily dose used. Based on the results of these studies, it was concluded that both insulin preparations showed expected efficacy in lowering blood glucose and that equivalent efficacy of insulin HM (ge) and HM (ss) was adequately confirmed.

In the clinical expert report in the 5-year renewal of marketing authorisation from 1993, 79 studies including a total of 3,059 patients that the MAH had performed in the given period were used as references. Based on these pharmacokinetic and pharmacodynamic studies and long-term studies involving transfer from HM (ss) to HM (ge) insulin and studies with the use of NovoLet only minor changes were recommended to the SmPC. For Actrapid®, the only suggested change was to include a recommendation to inject Actrapid® in the abdominal wall due to the delay in absorption in the deltoid region and the thigh.

Recently the MAH has performed sponsored trials in order to demonstrate efficacy and safety of the insulin analogue Insulin Aspart. In both Phase II and Phase III studies, Actrapid® was used as the comparator.

Three Phase III trials designed to evaluate the long-term safety and efficacy of Actrapid® and Insulin Aspart in Type I patients (035/EU and *036/USA)* and Type 2 diabetic patients (037/USA) were submitted in support of the application.

Study ID	Study locations	Design	Study Posology	Study Objective	Duration	Diagnosis Incl. criteria	Primary Endpoint
035/EU	Europe	Multicentre, multinational, randomised, parallel, open-labelled	A six-month multicentre, multinational, randomised, parallel, open-labelled, efficacy and safety comparison of insulin aspart (NovoRapid) and Actrapid® as meal-related insulin in a multiple-injection regimen in type I diabetic subjects	To evaluate the efficacy and safety of insulin aspart (NovoRapid) and Actrapid®	6 months (+ 1 month of run-in)	Type I diabetes (duration of at least 24 months)	HbA_{1c} after 6 months
036/US	USA	Multicentre, multinational, randomised, parallel, open-labelled	A six-month multicentre, randomised, parallel, open-label, efficacy and safety comparison of X14 and HI as meal-related insulin in a multiple-injection regimen in subjects with type I diabetes.	To evaluate the efficacy and safety of insulin aspart (NovoRapid®) and Actrapid®	6 months (+ 1 month of run-in)	Type I diabetes (duration of at least 24 months)	HbA_{1c} after 6 months
037/US	USA	Multicentre, multinational, randomised, parallel, open-labelled	A six-month multicentre, randomised, parallel, open-label, efficacy and safety comparison of X14 and HI as meal-related insulin in a multiple injection regimen in subjects with type 2 diabetes.	To evaluate the efficacy and safety of insulin aspart (NovoRapid) and Actrapid®	6 months (+ 1 month of run-in)	Type II diabetes (duration of at least 24 months)	HbA_{1c} after 6 months

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)

Pivotal trials 035/EU, 036/USA and 037/USA

Methods (including study design, blinding, randomisation, treatments, objectives and endpoints)

These three phase III trials were multi-centre, randomised, open label, parallel active-controlled 6-month comparisons designed to evaluate the long-term safety and efficacy of Actrapid® and Insulin Aspart in Type I DM patients (035/EU and *036/USA)* and Type 2 DM patients (037/USA).

The trials were designed to enrol a wide variety of Type I and Type 2 DM patients, excluding those anticipated either to have substantial endogenous insulin production, to be severely insulin resistant,

or to have poor compliance to Actrapid®, and those with poor function of organ systems involved in drug/glucose metabolism.

Randomisation was 1:2 (Actrapid®: Insulin Aspart), except for the Type 2 trial, in which the number of patients was smaller and randomisation was 1:1 to preserve statistical power.

After a 1 month run-in period, the patients were randomised and monitored during a six month maintenance period.

The primary endpoint was HbA_{1c} (reflecting 8-12 weeks' glycaemic control) and the secondary endpoints were fasting blood glucose, overall 23-hour glucose control as assessed by measuring serum glucose excursions above and below predefined targets concentration of 4-7 mmol/l, and self-measured 8-point BG profiles.

Results

Participant flow

The total number of Type 1 DM patients treated with Actrapid® in the intention-to-treat analysis was 624 (Studies 035/EU and 036/USA) and there were 86 Type 2 DM patients (study 037/USA).

Baseline data

In the table below, baseline characteristics for the ITT population for all three trials (035/EU, 036/USA and 037/USA) are presented.

Table 3-1 Demographic and baseline characteristic of subjects in the Phase III trials (ITT population)

	Type 1 Diabetic Subjects				Type 2 Diabetic Subjects	
	036/USA		035/EU		037/USA	
	IAsp	HI	IAsp	HI	IAsp	HI
Number of Subjects Exposed						
N	587	279	698	349	90	87
Age (yrs)						
N	587	279	698	349	90	87
Mean (SD)	39.0(10.6)	40.0(12.0)	37.6(11.3)	38.2(11.9)	56.7(9.8)	58.0(10.0)
Median	38.5	38.9	35.9	36.4	57.0	58.1
Min-Max	19.1-76.1	18.2-77.3	18.1- 4.7	18.2-70.7	34.5-75.9	38.0-77.3
Gender (N,(%))						
Male	299(51%)	148(53%)	383(55%)	192(55%)	56(62%)	51(59%)
Female	288(49%)	131(47%)	315(45%)	157(45%)	34(38%)	36(41%)
Race (N,(%))						
Caucasian	550(94%)	260(93%)	693(99%)	344(99%)	69(77%)	67(77%)
Black	11(2%)	7(3%)		1(<1%)	8(9%)	8(9%)
Asian	4(1%)	2(1%)	3(<1%)	3(1%)		
Other	22(4%)	10(4%)	2(<1%)	1(<1%)	13(14%)	12(14%)
BMI (kg/m^2)						
N	587	279	698	349	90	87
Mean (SD)	25.5(3.5)	25.7(3.2)	25.1(3.1)	24.9(3.0)	29.7(4.3)	29.3(4.3)
Median	25.1	25.7	24.7	24.8	29.4	29.0
Min-Max	17.9-37.6	17.7-33.8	17.8-36.0	17.9-34.5	20.2-39.5	20.2-39.7
Baseline HbA1c (%)						
N	587	279	698	349	90	87
Mean(SD)	7.90(1.13)	7.97(1.25)	7.96(1.16)	7.97(1.16)	8.11(1.18)	7.83(1.08)
Median	7.80	7.90	7.95	7.90	8.20	7.80
Min-Max	4.5-11	4.0-12	4.4-12	5.0-12	4.1-11	5.3-11
Duration of Diagnosed Diabetes						
N	587	279	698	349	90	87
Mean(SD)	15.7(9.7)	15.8(9.3)	14.8(10.1)	15.1(10.2)	12.8(7.7)	12.7(8.0)
Median	14.6	14.5	12.8	13.2	10.9	10.9
Min-Max	1.8-53.3	1.5-44.2	1.9-58.1	2.0-50.5	2.0-35.0	2.5-37.6
Number of Daily Basal Insulin Injections (N,(%))						
≤ 1	570(97%)	268(96%)	411(59%)	217(62%)	87(97%)	83(95%)
> 1	17(3%)	11(4%)	287(41%)	132(38%)	3(3%)	4(5%)

Cross Reference EOT Tables 1 and 2

Numbers analysed

Study 035/EU

A total of 1,070 patients were randomised, 708 to insulin aspart (NovoRapid) and 362 to Actrapid®. Of these, 1,065 were exposed to the trial drugs and constituted the safety population. The ITT population consisted of 1,047 patients (698 insulin aspart (NovoRapid®) and 349 Actrapid®) and the PP population of 1,006 patients (674 insulin aspart (NovoRapid®) and 332 Actrapid®). A total of 32 subjects withdrew during treatment with insulin aspart (NovoRapid) and 27 subjects withdrew during treatment with Actrapid®. Withdrawal reasons: The rates for AE and ineffective therapy were comparably low for both treatments, the most frequent reason for withdrawal was 'other' in 18 and 15 patients, respectively

(insulin aspart (NovoRapid), and Actrapid®, respectively) and 'non-compliance' in 6 subjects of the Actrapid® group.

Study 036/US

A total of 884 subjects were randomised, 597 to insulin aspart (NovoRapid®) and 287 to Actrapid®. Of these, 882 were exposed to study drug. The ITT population consisted of 866 patients (587 insulin aspart (NovoRapid) and 279 Actrapid®) and the PP population of 803 patients (546 insulin aspart (NovoRapid®) and 257 Actrapid). A total of 45 (7.6%) subjects withdrew during treatment with insulin aspart (NovoRapid®) and 24 (8.4%) subjects withdrew during treatment with Actrapid®. The withdrawal rates due to AE and ineffective therapy were comparably low for both treatments, the most frequent reason for withdrawal was 'other' in 30 and 19 patients respectively (insulin aspart (NovoRapid®), and Actrapid®, respectively) and 'non-compliance' in 9 subjects of the insulin aspart (NovoRapid®) group.

Study 037/US

A total of 182 subjects were randomised, 91 subjects to each of the 2 treatment groups. All of these were exposed to study drug. The ITT population consisted of 177 patients (90 insulin aspart (NovoRapid®) and 87Actrapid®) and the PP population of 156 patients (78 in each treatment group). A total of 3 (3.3%) subjects withdrew during treatment with insulin aspart (NovoRapid®) and 9 (9.9%) subjects withdrew during treatment with Actrapid®. Three patients from the Actrapid® group withdrew due to an AE (myocardial infarction, colon carcinoma, cerebrovascular disorder) and 4 due to 'other' reasons.

The treatment groups were well balanced with respect to age, gender, race, weight, height, BMI, and to smoking or not. The mean diabetes duration was in both groups about 13 years. Mean baseline HbA_{1c} was higher in the insulin aspart (NovoRapid®) group compared to the Actrapid® group (8.115 vs. 7. 87%). The mean doses of Actrapid®, and insulin aspart (NovoRapid®), respectively were similar at baseline, as well as were the mean doses of basal insulin.

2.6.5.3. Outcomes and estimation

Study 035/EU

The results of the efficacy parameters are shown below:

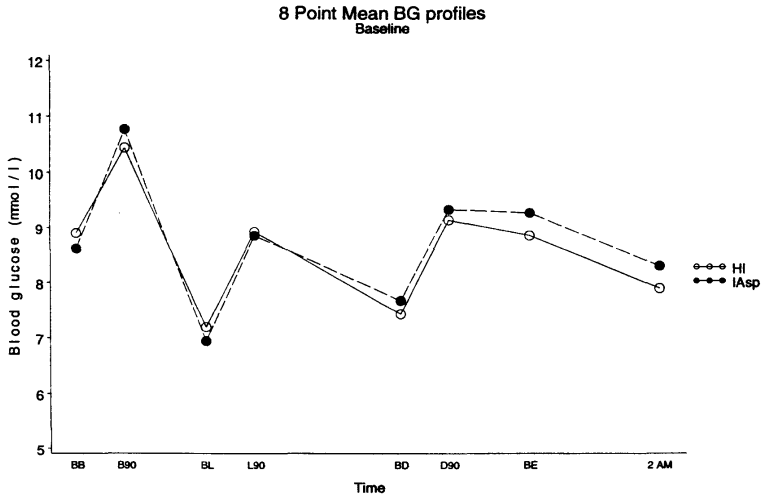
	IAsp			HI			IAsp-HI		
	N	Mean	(SEM)	N	Mean	(SEM)	Mean	95% C.I.	P-Value
HbA_{1c} (%)	694	7.88	(0.03)	346	8.00	(0.04)	-0.12	[-0.22 ;-0.03]	0.0137
Prandial BG Increment (mmol/l)	651	0.54	(0.09)	329	1.69	(0.12)	-1.15	[-1.43 ;-0.87]	0.0000
BG Variability (mmol/l)	623	2.78	(0.05)	315	2.84	(0.07)	-0.06	[-0.22 ; 0.10]	0.4890
Meal:basal Ratio	694	1.39	(0.02)	345	1.58	(0.03)	-0.19	[-0.25 ;-0.12]	0.0000
Total Insulin (U/kg)	695	0.71	(0.01)	348	0.69	(0.01)	0.02	[0.00 ; 0.04]	0.0148

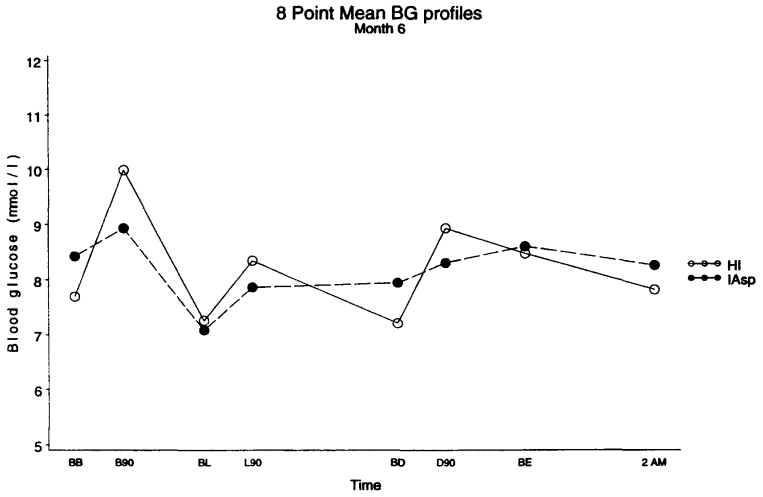
All adjusted for baseline value and centre

Mean HbA_{1c} after 6 months was slightly lower after treatment with insulin aspart (NovoRapid®) compared to treatment with Actrapid®. The difference was statistically significant in favour of insulin aspart (NovoRapid®). For both treatments, HbA_{1c}-levels remained relatively stable throughout the 6 months.

The mean 8-point BG profiles after 6 months of treatment were lower for Actrapid® before breakfast, before dinner and at 2 a.m. All mean 90-minutes postprandial BG values were Actrapidgher for Actrapid® compared to insulin aspart (NovoRapid®).

Please refer to the 2 figures below for the 8-point BG profiles at baseline and after 6 months of therapy, as well as to the table summarising the means at the different time-points.





ANOVA 8 point Blood Glucose (mmol/l) after 6 Months :

Time of Day	IAsp N	IAsp Mean (SEM)	HI N	HI Mean (SEM)	IAsp - HI Mean	95% C.I.	P-value
Before Breakfast	672	8.46 (0.13)	337	7.68 (0.18)	0.79	[0.36 - 1.21]	0.0003
Breakfast + 90 min	669	8.87 (0.15)	331	10.1 (0.21)	-1.20	[-1.68 - -0.71]	0.0000
Before lunch	671	7.13 (0.13)	336	7.31 (0.18)	-0.18	[-0.60 - 0.23]	0.3811
Lunch + 90 min	667	7.96 (0.12)	333	8.51 (0.17)	-0.55	[-0.96 - -0.15]	0.0068
Before Dinner	672	7.99 (0.13)	337	7.30 (0.18)	0.69	[0.25 - 1.13]	0.0020
Dinner + 90min	664	8.35 (0.14)	334	8.98 (0.19)	-0.63	[-1.07 - -0.18]	0.0056
Bedtime	670	8.71 (0.14)	336	8.68 (0.19)	0.04	[-0.42 - 0.49]	0.8728
2 am	647	8.44 (0.14)	325	8.05 (0.19)	0.39	[-0.05 - 0.83]	0.0816

The 95% confidence interval (C.I.) and p-values are based on an ANOVA with adjustment for baseline BG value and centre.

Study 036/US

The results of the efficacy parameters are shown below:

	IAsp		HI		IAsp-HI		
	N	Mean (SEM)	N	Mean (SEM)	Mean	95% C.I.	P-value
HbA1c (%)	585	7.78 (0.03)	278	7.93 (0.05)	-0.15	[-0.26;-0.05]	0.0048
Prandial BG increment (mmol/l)	552	0.12 (0.12)	259	1.58 (0.16)	-1.46	[-1.83;-1.09]	0.0000
BG variability (mmol/l)	548	3.21 (0.06)	253	3.31 (0.09)	-0.10	[-0.29; 0.10]	0.3277
Meal basal ratio	579	1.67 (0.03)	273	1.86 (0.05)	-0.18	[-0.29;-0.07]	0.0011
Total insulin (IU/kg)	579	0.71 (0.01)	277	0.69 (0.01)	0.03	[0.01; 0.05]	0.0048

All end-points adjusted for baseline value and centre - ITT analyses

Mean HbA_{1c} after 6 months was, as in 035/EU, slightly lower after treatment with insulin aspart (NovoRapid®) compared to treatment with Actrapid®. The difference was statistically significant in favour of insulin aspart (NovoRapid®). For both treatments, HbA_{1c}-levels remained relatively stable throughout the 6 months.

As in 035/EU, the mean 8-point BG profiles after 6 months of treatment were lower for Actrapid® before breakfast, before dinner and at 2a.m. All mean 90-minutes postprandial BG values were higher for Actrapid® compared to insulin aspart (NovoRapid®).

The prandial BG increments were similar to the ones in trial 035/EU, too, i.e. being lower for insulin aspart (NovoRapid®). The decrease in BG variability was similar in the insulin aspart (NovoRapid®) and the Actrapid® group.

The doses of meal related insulin remained almost constant over the treatment period as regards both treatment groups. The mean basal insulin doses increased slightly for both groups, for Actrapid® from 0.25 IU/kg at baseline and at 3 months) to 0.27 IU/kg at 6 months, and for insulin aspart (NovoRapid®) from 0.24 IU/kg to 0.27 IU/kg at 3 and 6 months. Accordingly, the meal-related to basal insulin ratio at 6 months was slightly lower in the insulin aspart (NovoRapid®) group compared to the Actrapid® group, and the total insulin dose higher for insulin aspart (NovoRapid®).

Study 037/US

The efficacy results for Study 037/US are shown in the table below.

Efficacy Results:

		IAsp			Actrapid®		IAsp-Actrapid®		
	N	Mean	(SEM)	N	Mean	(SEM)	Mean	95% C.I.	P-Value
HbA_{1c} (%)	90	7.70	(0.09)	86	7.82	(0.10)	-0.12	[-0.38 - 0.14]	0.3684
Prandial									
BG Increment (mmol/l)	87	1.20	(0.20)	82	1.32	(0.20)	-0.12	[-0.67 - 0.43]	0.6662
BG Variability (mmol/l)	85	2.49	(0.13)	80	2.78	(0.14)	-0.29	[-0.66 - 0.09]	0.1302
Meat-related/									
Basal Insulin Ratio	88	1.80	(0.11)	87	2.01	(0.11)	-0.21	[-0.50 - 0.08]	0.1524
Total Insulin	89	0.67	(0.02)	87	0.70	(0.02)	-0.03	[-0.08 - 0.01]	0.1747

All adjusted for baseline value and centre, (ITT population)

The efficacy results for the endpoints were comparable for Actrapid® and insulin aspart (NovoRapid), or to express it more correctly, insulin aspart (NovoRapid®) was not inferior to Actrapid® with respect to HbA_{1c} after 6 months, prandial BG increments, BG variability, the total insulin dose and the meal-related/basal insulin ratio. For both treatments, HbA_{1c}-levels remained relatively stable throughout the 6 months.

The means of the endpoints appeared for Actrapid® also to be roughly comparable with the means observed in the two studies including type I diabetes patients, apart from a higher meal-related/basal insulin ratio in this study.

2.6.5.4. Supportive study(ies)

Study NN729-1541

The overall objective of Trial NN729-1541 was to compare the efficacy and safety of Actrapid® produced by the current process and Actrapid® (NN729) in subjects with Type 1 DM (see Quality section for further details).

The overall objective of Trial NN729-1541 was to compare the efficacy and safety of Actrapid® produced by the current process and Actrapid® (NN729) in subjects with Type 1 DM (see Quality section for further details).

A total of 240 subjects with Type 1 DM; mean age 38.8 years; mean BMI 25.0 kg/m2; and mean HbA_{1c} 8.0% were randomised (1:1) and exposed to treatment with NPH insulin as basal insulin (1–3 times daily) and Actrapid® (NN729) (N=126) or Actrapid® (current process) (N=114) as bolus insulin. Overall, 92% of the subjects completed the trial.

In this study, there was no significant difference between the two treatment groups with regard to HbA_{1c} levels. The same applied to the ITT analysis set.

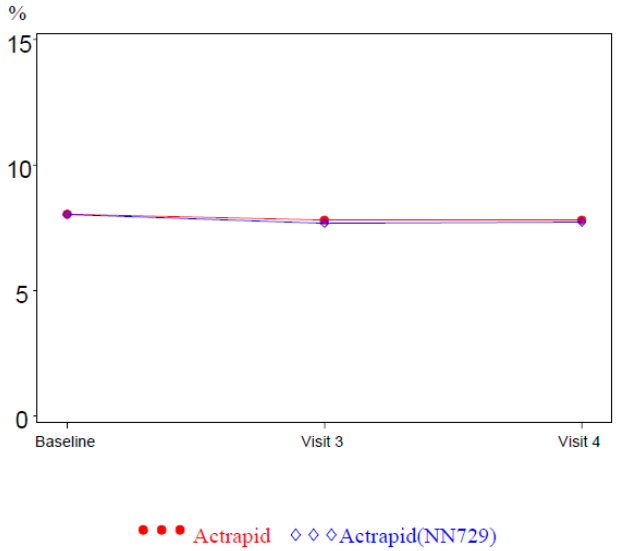


Figure 2–1 Mean HbA_{1c} Profiles PP Analysis Set

Fasting plasma glucose decreased slightly and evenly in both treatment groups during the course of the trial. There was no apparent difference between the two treatment groups at any of the visits.

2.6.6. Discussion on clinical efficacy

The clinical efficacy of Actrapid® was initially based on a small (13 patients) Phase II study and 5 Phase III studies with a total of 189 patients treated for 1 year in trials comparing insulin HM (ge) and insulin HM (ss) both for 100 U/ml and 40 U/ml. Based on the results of these studies, it was concluded that both insulin preparations including Actrapid® was efficacious in lowering blood glucose.

For the EU MAA in 2002, clinical efficacy was supported by 3 Phase III studies (Studies 035/EU, 036/US and 037/US) conducted in the US and in the EU and including both Type 1 DM patients and Type 2 DM patients.

All three studies (Studies 035/EU, 036/US and 037/US) were conducted according to the guidelines; designed as six-month multicentre, multinational, randomised, parallel, open-label, efficacy and safety studies.

The studies are all considered to be well performed in a representative population including both Type 1 and Type 2 DM patients. As the primary endpoint was HbA_{1c}, the open-labelled design is not expected to have influenced the study results in any clinically relevant degree. It is endorsed that both Type I DM and Type II DM patients were included. The 6-month study period is considered acceptable as the 6 months were preceded by a 1-month run-in period and further, the patients were to have been diagnosed (and thereby treated) for at least 24 months prior to enrolment.

Although the studies were unblinded the primary and secondary endpoints are considered robust.

Recommended injection site was abdomen for the meal-related insulin. The criteria for efficacy, both primary (HbA_{1c} at 6 months) and secondary endpoints (prandial BG increments after 3 meals and the variability of the 8-point BG profile) are considered appropriate.

In total 2,136 Type 1 DM and Type 2 DM patients were randomised and of these, 740 patients were randomised to Actrapid® treatment. Sixty (60) of the 740 patients were withdrawn; 8 due to adverse events, 5 due to ineffective therapy, 9 due to non-compliance and 38 for other reasons, including personal reasons, loss to follow-up and pregnancy. These numbers are considered acceptable for a long-term study of 6 months' duration. Overall, a sufficient number of patients were included in the trials, though the majority of the patients were included in the Type 1 DM trials (035/EU and 036/USA). Only 87 patients with Type 2 diabetes were treated with Actrapid®.

Both within the studies and across the studies, baseline characteristics were comparable between the treatment groups. Mean age was 37-40 years in the Type 1 DM patients and (as expected) slightly older in the Type 2 DM patients (56-58 years). The patients had on average had DM for 12-15.8 years; slightly longer in the Type 1 DM studies. Mean BMI was also higher in the Type 2 DM study (29 mg/m^2) compared with the corresponding BMI in the Type 1 studies (25 mg/m^2). Importantly, mean and median baseline HbA_{1c} was 7.80-7.97 among the Type 1 DM patients and 7.80-8.20 among the Type 2 DM patients, thus the majority of the patients were slightly dysregulated.

In all three studies, the majority of the patients were Caucasian and approximately 47% of the patients being females. In the Type 2 DM study, the proportion of males was higher (59-62%). Mean age at baseline was 37-40 years in the Type 1 DM studies and as could be expected slightly higher in the Type 2 DM study (56-58 years, Study 037/US).

The mean doses of Actrapid®, and insulin aspart (NovoRapid), respectively, were similar at baseline as well as were the mean doses of basal insulin.

Overall, across the trials and treatment groups HbA_{1c} remained mostly stable. For the primary endpoint, HbA_{1c} at 6 months, insulin aspart (NovoRapid) was statistically superior in both trials conducted with Type 1 DM patients (Study 035/EU and 036/US) however, the difference between the two treatments was small (0.12-0.15%). In Study 037/US including patients with Type 2 DM, the absolute difference between insulin aspart (NovoRapid) was of the same magnitude as observed in the Type 1 DM studies but in this study, the difference was not statistically significant. Overall, the observed differences between the treatments are not considered clinically significant.

Specific evaluation for the 3 studies is as follows:

<u>Study 035/EU:</u>

Throughout the study period (6 months), the HbA_{1c}-levels remained relatively stable though the mean HbA_{1c}-level was statistically significant lower for insulin aspart (NovoRapid) compared to Actrapid®.

Actrapid®'s BG profile at 6 months resembles the baseline profile which could be expected as therapy actually was unchanged. The lower BG values postprandial observed for insulin aspart (NovoRapid) are not unexpected due to the different time-action profile of Novorapid. Accordingly, also the BG increments from pre- to post-prandial were significantly lower for insulin aspart (NovoRapid) than for Actrapid®.

Despite lower prandial BG increments, the BG variability over the day did not differ for insulin aspart (NovoRapid) and Actrapid®.

At the 3- and 6-month time-points the basal insulin dose had in Study 035/EU slightly increased in the insulin aspart (NovoRapid) group.

<u>Study 036/US:</u>

Throughout the study period (6 months), the HbA_{1c}-levels remained relatively stable though the mean HbA_{1c}-level was statistically significant lower for insulin aspart (NovoRapid) compared to Actrapid.

Actrapid®'s BG profile at 6 months resembles the baseline profile which could be expected as therapy actually was unchanged. The lower BG values postprandial observed for insulin aspart (NovoRapid®) are not unexpected due to the different time-action profile of NovoRapid®. Accordingly, also the BG increments from pre- to postprandial were significantly lower for insulin aspart (NovoRapid®) than for Actrapid®.

Despite lower prandial BG increments, the BG variability over the day did not differ for insulin aspart (NovoRapid®) and Actrapid®.

At the 3- and 6-month time-points the basal insulin dose had in Study 036/USA slightly increased in both treatment group.

Study 037/US:

Compared with baseline HbA_{1c} levels only small changes were observed for both treatment groups; Mean HbA_{1c} declined marginally in the insulin aspart (NovoRapid) group and was stable in the Actrapid® group. At 6 months, there were no statistically significant difference between the treatment groups in any of the parameters presented in the table; especially, there were no statistically significant differences in neither HbA_{1c} nor total insulin.

In Trial NN729-1541, the two treatment groups were comparable with regards to demographic and diabetes characteristics.

Efficacy results from Trial NN729-1541 showed that there was no statistically significant nor clinically relevant difference between the two treatment groups (Actrapid® and Actrapid® (NN729)) with regard to HbA_{1c} levels and plasma glucose levels. It is concluded that the glycaemic control is similar for both treatments (Actrapid® and Actrapid® (NN729)).

Upon request, the MAH has presented efficacy data supporting the efficacy of Actrapid® in treatment of children and adolescent patients with diabetes mellitus. The clinical data presented by the MAH, included four Sponsor (Novo Nordisk) initiated studies where Actrapid® was used in the basal/bolus treatment of paediatric and adolescent patients aged 2-18 years. Study period was 24-30 weeks and the treatment were compared to other insulin-based therapies as placebo-controlled studies would be unethical. Overall, treatment with Actrapid® was shown to be efficacious. Individual dose titration resulted in appropriate decreases in HbA_{1c}, a validated and acceptable biomarker of effect in blood glucose levels. Changes in HbA_{1c} were non-inferior with Comparator.

As all four clinical studies described by the MAH only included paediatric patients with Type 1 DM, the MAH has not presented data supporting use of Actrapid® in the paediatric population with Type 2 DM. Considered that (insulin-treated) Type 2 DM is rare among paediatric patients and the magnitude of experience with Actrapid®-treatment of both (a) paediatric patients with Type 1 DM and (b) adult patients with Type 1 and Type 2 DM, this issue will not be pursued.

Taken together, the MAH has sufficiently documented the efficacy of Actrapid® in children and adolescent <18 years, and the Benefit-risk balance of Actrapid® when used in the treatment of diabetes mellitus is considered positive also for this population.

2.6.7. Conclusions on the clinical efficacy

In conclusion, the metabolic control reached in all three trials (Study 035/EU, 036/US and 037/US) is considered acceptable for both treatments indicating that Actrapid® is very effective in lowering blood-glucose in both paediatric and adult patients with Type 1 and Type 2 DM.

Results from Trial NN729-1541 demonstrated that the glycaemic control is similar for both treatments (Actrapid® and Actrapid® (NN729)).

2.6.8. Clinical safety

From the transfer studies from HM (ss) to 1Th1 (ge) there were no sign of toxicity related to HM (ge) from neither the adverse events nor from any laboratory abnormalities reported. Headache was reported from 7 in the HM (ge) group compared to 1 in the HM (ss) group, but all judged not to be related to insulin treatment. No increase or any differences were detected within or between the two treatment groups with respect to antibodies against insulin or yeast contaminants.

From the safety update related to the 5-year renewal of the marketing authorisation or the most recent periodic safety update report covering the period from 1 September 1998 to 30 June 2000 no new safety information has appeared that necessitates any change to the product information for Actrapid®.

2.6.8.1. Patient exposure

In the phase III program for insulin aspart (NovoRapid) there was a total of 687.3 and 360.4 patient years of exposure on insulin aspart (NovoRapid®) and Actrapid,® respectively.

2.6.8.2. Adverse events

Generally, Actrapid® was well tolerated and the safety profile was comparable between the two groups. Events, that occurred were all common conditions and symptoms and showed the same frequencies in both groups. Most common adverse events reported were upper respiratory tract infection (by more than 20% of patients in each treatment group), headache and accidental injuries (more than 10% of patients) pharyngitis, sinusitis, nausea, diarrhoea, and back pain (each more than 5% of patients).

Three (3) patients with malignant tumours were reported in the Actrapid® group (colon, larynx, and squamous cell carcinoma) and none in the insulin aspart (NovoRapid®) group while 6 reports on benign tumours were reported from each group. None of the malignant or benign tumours were considered to have causal relation to the drugs.

No local inflammation at the injection site was reported, but local lipodystrofia was reported in four and six patients on Actrapid® and insulin aspart (NovoRapid), respectively. One allergic reaction was reported considered probably or possible related in the Actrapid® group.

Hypoglycaemia

Hypoglycaemia is an expected event in the treatment of insulin requiring DM. In the table below, numbers of major hypoglycaemic events are presented. Major events comprised those patients that needed third party assistance or were hospitalised and given glucose or glucagon injections.

Table 4-3 Major hypoglycaemic events during treatment period – 035, 036, 037

	Phase III							
	Type 1 Diabetics 035 and 036 Combined				Type 2 Diabetics			
	Insulin Aspart		Actrapid		Insulin Aspart		Actrapid	
	N	(%) E	N	(%) E	N	(%) E	N	(%) E
Number of Patients Exposed	1303		644		91		91	
Baseline (Run-in Period)	87	(7%) 158	41	(6%) 72	1	(1%) 1	0	
Month 1	81	(6%) 135	38	(6%) 77	3	(3%) 3	1	(1%) 1
Month 2	80	(6%) 112	36	(6%) 72	2	(2%) 2	1	(1%) 1
Month 3	60	(5%) 94	36	(6%) 55	1	(1%) 1	2	(2%) 2
Month 4	55	(4%) 89	26	(4%) 42	3	(3%) 3	2	(2%) 3
Month 5	48	(4%) 87	25	(4%) 36	2	(2%) 2	0	
Month 6	36	(3%) 51	22	(3%) 26	1	(1%) 1	1	(1%) 1
After Month 6	7	(<1%) 12	1	(<1%) 1	0		0	
Treatment Period	216	(17%) 580	120	(19%) 309	9	(10%) 12	5	(5%) 8

The endpoint is number of hypoglycemic events within the last month.
One month corresponds to 30 days.
'After Month 6' includes patients on trial product where exposure time is greater than 6 months.
Run-in period in the phase III trials is from visit 2 until visit 3.
N = Number of patients with events
% = Proportion of exposed patients having the episode within the month
E = Number of hypoglycemic events

In total 120 (19%) Type 1 DM patients treated with Actrapid® experienced at least one major hypoglycaemic event (in total 309 events) with only 5 (5%) Type II diabetes patients had at least one similar event (in total 8 events). There was in both groups a tendency for the rate of events to decrease with time probably due to intensified treatment. Hypoglycaemic events tended to be more frequent during the night-time whereas no trend was seen for insulin aspart (NovoRapid). There was no significant difference between the two groups in frequencies of major hypoglycacmic events.

The incidence of minor hypoglycaemic events was markedly less for Type 2 patients (65%) than for Type 1 diabetic patients (80%). The overall frequency was similar between treatments for both patient groups.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

Throughout the development program, the incidence of SAEs was low in both treatment groups. The SAE incidence was 6% in the Actrapid® group and 4% in the insulin aspart (NovoRapid) group in the Type I DM population. In the Type II population, the corresponding rates were 8% and 7%, respectively.

Numbers of SAEs in the Actrapid® group were 53 in 45 patients in total for the 3 Phase III studies. One third of the SAEs were reported in the System Organ Class "Metabolic and Nutritional Disorders" and most of these related to the glycaemic control.

Altogether less than 1% of the exposed population reported SAEs in relation to glycaemic control and two patients in each group withdrew for that reason.

There were no differences in the profile or distribution of SAEs between treatment groups. Less than 2% of patients exposed had SAEs, which were considered to be probably, or possibly related to the trial product. All these were due to hypoglycaemic events.

The most frequent SAEs in Type I DM patients were related to glycaemic control, in Type II DM patients the most frequent SAEs were cardiovascular events, unlikely related to trial medication. No deaths occurred in the Actrapid® groups. Major hypoglycaemic events occurred less frequently in Type II DM patients.

In the table below incidence rates of severe adverse events are given for the combined phase lll program in Type 1 diabetic patients divided into various disorders.

Table 4-2 Serious adverse events incidence rates in Type 1 diabetic subjects 034/EU and 036/USA combined

	Phase III - Type 1 Diabetics 035 and 036 Combined					
	IAsp			HI		
	N	%	E	N	%	E
Number of Subjects Exposed	1303			644		
All Serious Adverse Events	58	4	66	36	6	41
System Organ Class:						
Metabolic and nutritional disorders	28	2	29	12	2	15
Gastro-intestinal system disorders	6	<1	6	4	<1	4
Secondary terms	6	<1	6	1	<1	1
Resistance mechanism disorders	5	<1	5	.	.	.
Body as a whole - general disorders	4	<1	4	2	<1	2
Myo endo pericardial & valve disord	2	<1	3	4	<1	5
Psychiatric disorders	2	<1	3	1	<1	1
Respiratory system disorders	2	<1	2	2	<1	2
Urinary system disorders	2	<1	2	1	<1	1
Application site disorders	1	<1	1	.	.	.
Centr & periph nervous system disor	1	<1	1	2	<1	2
Foetal disorders	1	<1	1	.	.	.
Neoplasm	1	<1	1	3	<1	3
Vascular (extracardiac) disorders	1	<1	1	1	<1	1
Vision disorders	1	<1	1	1	<1	1
Liver and biliary system disorders	.	.	.	1	<1	1
Musculo-skeletal system disorders	.	.	.	1	<1	1
Reproductive disorders, female	.	.	.	1	<1	1

N = Number of subjects
% = Proportion of exposed subjects having the event
E = Number of adverse events

Deaths

Across the trials 035/EU, 036/US and 037/US, no deaths occurred in the Actrapid® group.

2.6.8.4. Laboratory findings

Across the trials 035/EU, 036/US and 037/US, there was no consistent trends or significant changes from baseline in any of the clinical laboratory tests.

2.6.8.5. Discontinuation due to adverse events

Less than 1% of Type I DM patients in either treatment group in these trials withdrew due to AEs; for detail see table below. A total of 5 Type I DM patients in the Actrapid® group and 9 in the insulin aspart (NovoRapid) withdrew due to 5 and 11 AEs, respectively.

Four (4) of the AEs in the Actrapid® group was reported as SAEs: 2 episodes of hypoglycaemia - both probably related to trial product, 1 malignant larynx neoplasm, and 1 angina pectoris (both unlikely related to trial product).

In Type II DM patients, 3 subjects experienced AE related withdrawals in the Actrapid® group due to colon carcinoma, cerebrovascular disorder, and myocardial infarction. All three were severe and reported as SAEs but not considered likely to be related to Actrapid® treatment. No Type II DM patients were withdrawn due to AEs in the insulin aspart (NovoRapid) group.

Table 4-1 Adverse events leading to withdrawal in the phase III trials 035/EU and 036/USA combined

	Incidence of Events			
	Type 1 Diabetic Subjects		Type 2 Diabetic Subjects	
Preferred Terms	IAsp	HI	IAsp	HI
Number of Subjects Exposed	1303	644	91	91
Number of subjects withdrawn due to AEs	9 (<1%)	5 (<1%)	0	3 (3%)
Angina pectoris		1		
Cerebrovascular disorder				1
Colon carcinoma				1
Coma hypoglycaemia	1			
Coronary artery disorder	1			
Fatigue	2			
Headache	1			
Hypoglycaemia		2		
Injury accidental	1			
Ketosis	1			
Larynx neoplasm malignant		1		
Myocardial infarction	1			1
Nausea	1			
Neuropathy		1		
Urticaria	1			
Weight increase	1			

2.6.8.6. Post marketing experience

Actrapid® has been marketed for several decades and manufactured by genetic engineering since 1988. Post-marketing safety reporting was addressed in a specific five-year safety update for biosynthetic human insulin for the period from 1.3.1993 to 31.8 1998. An estimated total of 21 million person-years of exposure were accumulated during the 5-year period of review, representing a minimum of 4 million individual patients. A total of 5.986 adverse events of which 523 were serious adverse events were reported. A review of these indicated that the events were either adverse drug

reactions that were already in the current core data sheet or cases for which an alternative cause was more likely. Two safety issues were examined specifically:

1) A toxicology study has shown a statistically significant increased incidence of mammary gland tumours in female Sprague-Dawley rats receiving high doses of Actrapid® (75 IU/kg)/bid). It is well known that this rat-strain is prone to get mammary tumours and an extensive literature review did not find any evidence to support the finding. It was concluded that the finding was strain specific and no further studies were recommended. There was no finding in the period of adverse event reporting of mammary tumours, which support the above conclusion.

2) Another literature safety-review was performed in the period based on some casuistic reports of change in hypoglycaemic symptoms after transfer to human insulin from animal originated insulin. There was neither in the literature nor in later studies any evidence of this phenomenon. However, a changed symptomatology can be seen after intensifying the metabolic control that in some patients may lead to hypoglycaemic unawareness.

Another PSUR for fast acting insulin from the period from 1.9 1998 to 30.6.2000 representing 638 AEs of which 108 were categorised as SAEs is performed by Novo Nordisk for this application. That report represents 2,14 million person-years of exposure representing a minimum of over 1 million individual persons in market experience. 3,000 patients have received fast acting human insulin in period of review. 638 adverse events were reported in the period of which 108 were serious adverse events.

Of these 108 cases 29 cases were classified as serious unlisted and each of these are analysed in the report. Some of these resulted in specific literature review and consultation with specialists.

1) Some reports from Japan have suggested that insulin produced on Saccharomyces cerevisiae (baker's yeast) may cause impaired liver function. Novo Nordisk has received 58 reports on impaired liver function since 1987 of which 54 (25 serious) came from Japan. Several facts seem to contradict the above hypothesis. Many of the reports are on insulin HM (SS), which is not produced by this technology. Assessing the individual cases, they do not support the hypothesis of a Type 2 idiosyncratic reaction as biopsies were without eosinophil granulocytes, liver enzymes did increase immediately and no other signs of allergy were seen.

Based on the specific cases studied the conclusion in the PSUR that no areas of major concern have been identified in the period of review is fully supported, and no further amendments to the core labelling are required at present for safety.

The most frequent adverse event reported is still unacceptable change in blood glucose either as hyperglycaemia or hypoglycaemia. These events are the consequence of inappropriate insulin dosing compared to the individual patient need in a given situation.

It should be noted that a much lower incidence of hypoglycaemia is seen in the PSUR than reported here from the clinical trials. This is of course just reflecting the difference in which these events are reported and in real life the figures from our clinical trials are more reflecting real life although there may be an over reporting in clinical trials.

A safety issue that has been discussed since the day of first marketing of human insulin is the inclusion of an improved warning concerning driving or operating machines in case of a hypoglycaemic event. This warning was agreed between the authorities and the marketing authorisation holders of insulin products in EU and implemented in the Actrapid® SmPC in 1998. It seems fair to have a warning concerning driving as hypoglycaemia is a condition that potentially impair the ability to drive or use other machinery and it is known from studies to cause poor steering, increased swerving and spinning, poor road positioning and compensatory slow driving. However, diabetic drivers do not seem to be involved in more accidents than the non-diabetic population.

SAFETY DATA FROM TRIAL NN729-1541

The overall objective of Trial NN729-1541 was to compare the efficacy and safety of Actrapid® produced by the current process and Actrapid® (NN729) in subjects with type 1 diabetes (see Quality section for further details).

Adverse events

Incidences of adverse events reported during treatment with Actrapid® or Actrapid® (NN729) in trial NN729-1541 are presented in the table below.

Table 2–2 Overview of Treatment Emergent Adverse Events (Trial NN729-1541)

	Actrapid N	(%)	E	Actrapid(NN729) N	(%)	E
Subjects Exposed	114			126		
All Adverse Events	63	(55.3)	165	84	(66.7)	270
Serious Adverse Events	6	(5.3)	7	14	(11.1)	18
Deaths	1		1	1		1
Severe Adverse Events	6	(5.3)	7	9	(7.1)	13
Adverse Events Possibly or Probably Related to trial Product	7	(6.1)	8	17	(13.5)	20
Adverse Events leading to Withdrawal	2	(1.8)	3	4	(3.2)	4

N: Number of subjects with adverse event
%: Proportion of subjects having the event
E: Number of adverse events

Hypoglycaemia

In total, hypoglycaemia was observed in 2 subjects in the Actrapid® (NN729) group and in 4 subjects in the Actrapid® group, of which 2 incidences in each group were assessed as possibly or probably related to trial product (see table below).

Table 2–5 Hypoglycaemic episodes during treatment with trial product (NN729-1541)

	Actrapid N	(%)	E	Actrapid(NN729) N	(%)	E
No. of Subjects Exposed	114			126		
Hypoglycaemic Episodes	85	(74.6)	1003	99	(78.6)	1261
Major	8	(7.0)	17	15	(11.9)	45
Minor	76	(66.7)	700	82	(65.1)	773
Symptoms only	47	(41.2)	270	61	(48.4)	410
Unknown	13	(11.4)	16	16	(12.7)	33

N: Number of subjects with hypoglycaemic episodes
%: Proportion of subjects with hypoglycaemic episodes
E: Number of hypoglycaemic episodes

Serious adverse events and deaths

In Trial NN729-1541, the proportion of subjects having experienced a serious adverse event was 11% in the Actrapid® (NN729) group and 5% in the Actrapid® group and less than 10 subjects in each group experienced severe adverse events during the trial. Two deaths were reported in NN729-1541; one in each treatment group. For both deaths, the investigator and the sponsor evaluated the causality to be 'unlikely' to be related to trial product.

Immunogenicity

Insulin human antibody formation did not change significantly in either treatment group during the trial.

2.6.9. Discussion on clinical safety

In the three Phase III studies (035/EU, 036/US and 037/US), the overall exposure for Actrapid® is 360.4 patient years. This is considered acceptable. Data from previous studies and 'real-life' use also support a mild safety profile with hypoglycaemia being the most important identified risk.

There were no notable differences between the safety profile of insulin aspart (NovoRapid) and Actrapid®. The most commonly reported AEs were related to upper respiratory tract infections and are most likely natural occurring seasonal infections and not related to the insulin treatment. Likewise, it is agreed that none of the cases of neither malignant nor benign tumours are expected to be related to the insulin treatment.

Only few patients reported local lipodystrophy at injection site. This is a well-known adverse reaction to repeated subcutaneous insulin injections and patients are instructed to alter injection site (within the abdominal area). It is expected that the frequency of local injection site lipodystrophy would increase with increasing study period. Nevertheless, it is reassuring that it was only reported in few (Actrapid®-treated) patients.

As expected episodes of hypoglycaemia were reported in both treatment groups. It is reassuring that there was no difference in frequency between the two treatments (insulin aspart (NovoRapid®)) and Actrapid®). As expected, hypoglycaemia was reported with a higher frequency among patients with Type 1 DM compared to patients with Type 2 DM.

Lipodystrophy is a well-known adverse reaction to repeated subcutaneous insulin injections and patients are instructed to alter injection site (within the abdominal area). It is expected that the frequency of local injection site lipodystrophy would increase with increasing study period. Nevertheless, it is reassuring that it was only reported in few (Actrapid®-treated) patients.

Across the Phase III trials, only 8 patients treated with Actrapid® withdrew due to (S)AEs. Of these 8 patients, only 2 cases of hypoglycaemia were considered related to study drug.

The majority of SAEs were within the SOC "Metabolic and Nutritional Disorders" and were (not surprisingly) related to hypoglycaemic episodes. Episodes of hypoglycaemia were reported in both treatment groups. It is reassuring that there was no difference in frequency between the two treatments (insulin aspart (NovoRapid) and Actrapid®). As expected, hypoglycaemia was reported with a higher frequency among patients with Type 1 DM compared to patients with Type 2 DM. Immunogenicity has been a well-characterised risk for more than a decade. The overall risk is low. Several studies have investigated the risk of developing antibodies to human insulin during treatment with insulin products including Actrapid® and studies in patients, including adolescent patients, treated with Actrapid® have shown, that the antibodies often are transient and does not impact the effect of treatment.

It is reassuring that no patients included in studies 035/EU, 036/US and 037/US died.

Post-approval data for the period from 1.3.1993 to 31.8 1998 include data from a minimum of 4 million individual patients providing data from an estimated total of 21 million-person years of exposure. The MAH informs that no new safety issues were revealed with the most commonly reported SAE being hypoglycaemia. This (S)AE is a well-known (S)AE to all insulins and as such not solemnly related to Actrapid®. The SmPC adequately addresses this issue both in section 4.4 and in section 4.8.

Upon request, the MAH has presented safety data for Actrapid® when used in paediatric and adolescent patients. Based on four clinical studies, the most common AEs were reported to be respiratory tract infections, nasopharyngitis 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 four studies, the majority of hypoglycaemic events were mild and only few were considered serious. Other treatment-related AEs included administration site reactions, but these are not directly described in the MAH's response. As administration site reactions are known AEs to all insulin treatment which is administered subcutaneously, and there are no reports on administration site reactions being more commonly reported in association with Actrapid® compared to other s.c. administrated insulin products, this will not be pursued.

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', 'Investigations', 'General disorders and administration site conditions' and 'Injury, poisoning and procedural complication'. The most commonly reported PTs were all related to the pharmacodynamic mechanism of Actrapid® and included 'Blood glucose increased', 'Hypoglycaemia', 'Hyperglycaemia' and 'Drug ineffective'. Both the overall AEs picture based on SOCs and on PTs are rather consistent with the picture observed among adults and notably, the majority (69%) of all reported Es were non-serious. The small 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.

The MAH has sufficiently documented the safety of the Actrapid® used among children and adolescent <18 years, and the safety profile of Actrapid® when used in the treatment of diabetes mellitus is considered acceptable also for this population.

Overall, the current SmPC is considered being up-to-date and includes all relevant AEs in the tabulated list of adverse reactions in section 4.8. Likewise, relevant warning and precautions for use are sufficiently addressed in section 4.4. There is currently no need for amendment to the SmPC.

In Trial NN729-1541, the two treatment groups were comparable with regards to demographic and diabetes characteristics.

Overall, there were no clinically meaningful differences between the adverse event profile of the two treatments though more patients treated with Actrapid® (NN729) compared to patients treated with Actrapid® experienced adverse events (67% vs. 55%). In both treatment groups, the most frequently reported adverse events were within the SOC infections and infestations (≈23.5%), most often related to upper respiratory tract infections in both treatment groups. Importantly, the majority of these events were of mild or moderate severity.

Likewise, serious adverse events were reported in twice as many patients treated with Actrapid® (NN729) compared to patients treated with Actrapid® (14 vs. 6 patients, 18 vs. 7 events in the Actrapid® (NN729) and the Actrapid® treatment groups, respectively). There was no distinct pattern of the serious adverse events, though the difference was also (partly) due to more hypoglycaemic episodes in the Actrapid® (NN729) treatment group. Major hypoglycaemic episodes were reported in 45 vs. 17 patients (410 vs. 270 episodes), respectively in the Actrapid® (NN729) and the Actrapid® treatment groups, respectively. Of note, the total number of events/year is still small (in both treatment groups) and as the MAH states that *"it is not possible to give any firm explanation to the relative low reporting rate in the Actrapid® treatment arm in the NN729-1541 study"*, the issue will not be pursued.

It is reassuring that there were no significant nor clinically relevant changes in insulin human antibody formation in either treatment group during the trial.

2.6.10. Conclusions on the clinical safety

The most commonly reported adverse event related to the treatment with Actrapid® is hypoglycaemia. Cases are however not frequent and though potentially serious in nature, it can be managed with glucose-intake. Treatment with Actrapid® is considered safe. The applicant has also presented safety data for use of Actrapid® in patients with impaired renal function and in the paediatric population and overall, the safety profile in these special populations is comparable with adults (with normal renal function). Taken together, the safety profile of Actrapid® is well-characterised and acceptable.

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 2-8ºC followed by 4 weeks below 30ºC) 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. 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-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 assessment of the efficacy of Actrapid® is based on previously submitted studies comparing Actrapid® and NovoRapid (insulin aspart, a human insulin analogue). Three phase III studies comparing Actrapid® with Novorapid investigating the efficacy and safety of the products were provided.

These three phase III trials were multi-centre, randomised, open label, parallel active-controlled 6-months' comparisons designed to evaluate the long-term safety and efficacy of Actrapid® and Insulin Aspart in Type I DM patients (035/EU and 036/USA) and Type 2 DM patients (037/USA).

The primary endpoint was HbA_{1c} (reflecting 8-12 weeks' glycaemic control) and the secondary endpoints were fasting blood glucose, overall 23-hour glucose control as assessed by measuring serum glucose excursions above and below predefined targets concentration of 4-7 mmol/l, and self-measured 8-point BG profiles.

The metabolic control reached in all three trials (Study 035/EU, 036/US and 037/US) is considered acceptable for both treatments indicating that Actrapid® is very effective in lowering blood glucose in both Type 1 DM and Type 2 DM patients.

3.2. Favourable effects

Both within the studies and across the studies, baseline characteristics were comparable between the treatment groups. The majority of the included patients were Caucasian, mean age was 37-40 years in the Type I DM patients and (as expected) slightly older in the Type II DM patients (56-58 years). The patients had on average had DM for 12-15.8 years; slightly longer in the Type I DM studies. Importantly, mean and median baseline HbA_{1c} was 7.80-7.97 among the Type I DM patients and 7.80-8.20 among the Type II DM patients thus at baseline, the majority of the patients were slightly dysregulated. The mean doses of Actrapid®, and insulin aspart (NovoRapid®), respectively, were similar at baseline as well as were the mean doses of basal insulin.

Overall, across the trials and treatment groups HbA_{1c} remained mostly stable. For the primary endpoint, HbA_{1c} at 6 months, insulin aspart (NovoRapid) was statistically superior in both trials conducted with Type I DM patients (Study 035/EU and 036/US), however, the difference between the two treatments was small (0.12-0.15%). In Study 037/US including patients with Type II DM, the absolute difference between insulin aspart (NovoRapid) was of the same magnitude as observed in the Type I DM studies but in this study the difference was not statistically significant. Overall, the observed differences between the treatments are not considered clinically significant.

Efficacy results from Trial NN729-1541 showed that there was no statistically significant or clinically relevant difference between the two treatment groups (Actrapid® and Actrapid® (NN729) with regard to HbA_{1c} levels and plasma glucose levels. It is concluded that the glycaemic control is similar for both treatments (Actrapid® and Actrapid® (NN729).

Clinical and post-marketing data support a beneficial effect of Actrapid® treatment of children and adolescent patients with diabetes mellitus.

3.3. Uncertainties and limitations about favourable effects

None

3.4. Unfavourable effects

Lipodystrophy is a well-known adverse reaction to repeated subcutaneous insulin injections and patients are instructed to alter injection site (within the abdominal area). It is expected that the frequency of local injection site lipodystrophy would increase with increasing study period. Nevertheless, it is reassuring that it was only reported in few (Actrapid®-treated) patients.

The most commonly and severe reported adverse events related to the treatment with Actrapid® is hypoglycaemia. Cases are however not frequent and though potentially serious in nature can be managed with glucose intake. Immunological events are also potentially serious but only rarely reported. Overall, the current SmPC sufficiently addresses the adverse event profile of Actrapid®.

In Trial NN729-1541, serious adverse events were reported in twice as many patients treated with Actrapid® (NN729) compared to patients treated with Actrapid® (14 vs. 6 patients, 18 vs. 7 events in the Actrapid® (NN729) and the Actrapid® treatment groups, respectively). There was no distinct pattern of the serious adverse events, though the difference was also (partly) due to more hypoglycaemic episodes in the Actrapid® (NN729) treatment group. Major hypoglycaemic episodes were reported in 45 vs. 17 patients (410 vs. 270 episodes), respectively in the Actrapid® (NN729) and the Actrapid® treatment groups, respectively. Of note, and reassuringly, the total number of events/year is still small.

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 all patients with diabetes mellitus, 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 primary endpoint, HbA_{1c} at 6 months, where Actrapid® reached glycaemic control, indicating that Actrapid® is very effective in lowering blood glucose in both type 1 and type 2 DM patients. The evidence of efficacy provided in the three trials was considered convincing.

As for the unfavourable effects the most important and severe effect is not surprisingly recorded events of hypoglycaemia, which in few cases can be serious. Hyperglycaemia were also reported. Other less severe adverse events were related to local administration site reactions including redness, pain and itching.

3.6.2. Balance of benefits and risks

The observed metabolic control that was achieved in all three trials, is considered clinically relevant, as the glycaemic control was reached at 6-month trough evaluation of HbA_{1C}. The evidence provided is considered convincing. The safety profile of human insulin products is well characterised with more than 30 years of post-marketing experience globally.

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 Actrapid® 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 Actrapid® 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 Actrapid®. 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. Actrapid® 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 Actrapid® 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 Actrapid® 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.