SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Forcaltonin. This scientific discussion has been updated until 1 July 1999. For information on changes after this date, please refer to module 8B.

1. Introduction

The active ingredient of Forcaltonin is a recombinant salmon calcitonin (rsCT), a 32-amino acid peptide hormone that is structurally identical to chemically synthesised salmon calcitonin. Chemically synthesised salmon calcitonin (ssCT) has been in widespread clinical use for more than 20 years. Due to its high biological potency in man, calcitonin derived from salmon (sCT) is the most widely used therapeutic calcitonin agent for medicinal situations, where calcitonin is indicated.

Regarding pharmaceutical form and sCT content, Forcaltonin is comparable to conventional sCT preparations.

Forcaltonin is presented in single use glass ampoules as two dosage forms, 100 IU in 1 ml and 50 IU in 0.5-ml acetate buffer for subcutaneous, intramuscular or intravenous injection.

The approved indications are (dose range): Paget's disease of bone (50 IU x3/week to 100 IU/day), and Hypercalcaemia of malignancy (400 IU to 10 IU/kg q.i.d.).

2. Chemical, pharmaceutical and biological aspects

Active substance

Salmon calcitonin is a single chain 32 amino acid peptide hormones, with a disulfide bridge between the cysteine residues at sequence positions 1 and 7. A C-terminal glycine-extended rsCT precursor sequence is expressed in E. coli as a fusion protein A major structural feature of salmon calcitonin, which is important for full biological activity, is a prolinamidyl residue at the C-terminus, position 32. Since E. coli does not have the capability for this post-translational C-terminal amidation the glycine-extended precursor is amidated in vitro by an α-amidating enzyme (α-AE), obtained by rDNA technique in CHO-cells.

Data demonstrating the genetic stability of the production organisms during the optimised fermentation conditions were satisfactory.

Characterisation and authenticity in comparison with ssCT

The aim of the characterisation studies of rsCT is to prove authenticity in comparison with synthetic salmon calcitonin (ssCT). Other important features considered were the impurity profile and the degradation behaviour.

Since rsCT is a relatively small peptide it has been possible to clarify its structure in detail using a variety of physicochemical methods and to prove its authenticity with respect to ssCT.

The different production principle of rsCT and ssCT inevitably leads to a different impurity profile. However the company has used the strategy of removing the impurities, including related peptides, and has performed studies to examine the impurity profile.

In contrast to most other products derived from rDNA technology recombinant salmon calcitonin (rsCT) is a peptide with relatively few amino acids (32) in a single chain. In addition CT tolerates relatively harsh conditions during purification. Owing to the small size of the CT peptide the separation of macromolecular impurities should be possible to a greater extent than it is the case with larger proteins derived from rDNA technology.

Synthetic calcitonin (ssCT) is covered by the monograph calcitonin (salmon) of the Ph.Eur. As only certain Ph.Eur criteria on ssCT are applicable the company established a specific test programme dedicated to rsCT. Nevertheless, some of the Ph.Eur. criteria are applied also for rsCT.

Routine identification is performed by a combination of tryptic mapping with comparison of the retention times monitored by RP-HPLC and CEX-HPLC. This combination of methods together with the potency evaluation (in vitro assay) constitutes a reliable identity test.

Characterisation studies have been performed on in-house standard batches Comparisons were made to the Second International Standard for Calcitonin. Synthetic sCT from other sources of currently marketed products were also included for comparison.

Other comparative pharmacokinetic and pharmacodynamic studies have been performed to support authenticity (see sections 3 and 4).

The structure of rsCT has been unequivocally determined. The in vitro and in vivo assay data support the authenticity and full bioactivity of rsCT.

Finished product

The composition of Forcaltonin is similar to that of currently marketed products containing synthetic salmon calcitonin as active ingredient.

The list of specifications and routine tests is in line with current guidelines. Where necessary the company uses the general methods given in the Ph. Eur.

The identity and content of the active ingredient are determined chromatographically, using isocratic cation exchange HPLC (CEX-HPLC). A positive result in the in vivo potency assay is currently considered as part of the identification.

The rat bioassay according to the Ph. Eur. monograph for Calcitonin (salmon) is performed by the company as a routine procedure.

Pharmaceutical development

Forcaltonin is presented as a solution for injection in single-dose glass ampoules. An overage of the active ingredient is included.

Manufacture and control

The bulk active ingredient is manufactured by Unigene and transported to the manufacturing site at which the finished product is produced. The manufacturing process is a conventional one and has been described in sufficient detail.

Stability

Stability of the active ingredient

The batch results obtained so far are satisfactory and show that the active ingredient can be stored at either –20°C or at 2°C – 8°C. . It should be noted that satisfactory results after storage at 2° - 8 °C (the conditions quoted in the Ph.Eur. for synthetic calcitonin) confirm equivalency.

Stability tests on the finished product

Batches of the finished product are currently undergoing stability trials.

As a consequence of the analysis of these data, a shelf-life of 2 years at 2 - 8°C for the finished products can be given at present.

Evaluation of the viral safety

The CHO master cell bank (MCB) containing the expression construct for α-AE, used as a reagent in the downstream process, has been closely examined for contamination with viral agents. Particular attention was paid to the investigation of potential retrovirus contamination of the MCB No evidence of viral contamination has been found.

Data supporting the test strategy and the virus validation studies were considered satisfactory.

The raw materials of mammalian origin represent defined proteins from bovine sources obtained from suppliers within the United States or from countries considered to be BSE/TSE-free, and collected from herds free from infectious bovine viruses, or from certified human plasma.

Summary and conclusion on chemical and pharmaceutical aspects

Authenticity of the produced recombinant salmon calcitonin in regard to synthetic salmon calcitonin was demonstrated.

The responses provided by the Applicant to the Consolidated List of Questions are considered to be satisfactory. Certain issues are to be addressed on an ongoing basis as follow-up measures.

A consistent production process for rsCT is used. The fermentation process has been adequately validated.

At the beginning of September 1998, the company submitted to all CPMP Members an expanded data set on the α-AE. After analysis of the data set, the company proposes to revise the α-AE release- and in-process control specifications. This proposal has been accepted.

As a consequence of the satisfactory revision of the limits for the α-AE, there are no remaining objections with regard to part II of the dossier that need to be resolved before a marketing authorisation can be given.

As indicated above, certain issues are to be resolved on an ongoing basis as follow-up measures. The company has submitted a commitment to resolve these points, together with a proposal for the time frame.

3. Toxico-pharmacological aspects

Complete identity to conventional sCT and an even higher degree of purity are reported by the applicant, therefore with Forcaltonin a limited amount of pharmaco-toxicological testing was performed to supplement the literature data provided. The results of this supplementary testing confirmed the acceptability.

In pharmaceutical form and sCT content Forcaltonin is identical to conventional sCT preparations.

Pharmacodynamics

In rats rsCT induced a dose dependent decrease of serum calcium comparable to both the 2nd International Standard (2nd IS) and conventional sCT. Also other pharmacodynamic responses were similar between sCT and rsCT, including a similar cAMP increase, identical rates of development and disappearance of hypocalcaemia, the same maximum hypocalcaemic effect and the same area above the intensity curve. The comparable hypocalcaemic activity of sCT and rsCT was also demonstrated in dogs.

With respect to general pharmacodynamic investigations, rsCT and CT did not exert any relevant effects on general performance and behaviour of mice in doses 200 times that of therapeutic use. In dogs, there was neither electrocardiographic evidence of cardiotoxicity, nor evidence of adverse effects on blood pressure and heart rate after escalating intravenous doses of rsCT or sCT.

Experiences with sCT do not report clinically important drug interactions. No studies of this type were performed with Forcaltonin.

Pharmacokinetics

Pharmaco- and toxicokinetic aspects of rsCT in comparison with sCT have been studied in rats and dogs using a sensitive and specific radioimmunoassay (RIA) in single dose studies. The different investigations consistently characterised the pharmacokinetic properties of rsCT as being completely equivalent to established sCT.

The substance was rapidly absorbed. Dose-linearity after subcutaneous administration was established. rsCT was rapidly cleared from plasma (elimination half-life ≤ 110 min).

Rats and dogs were exposed to large multiples of therapeutic rsCT plasma concentrations particularly after intravenous administration.

Toxicology

Acute toxicity

One study used escalating intravenous doses up to 67 µg/kg body weight in dogs. No mortality occurred. Clinical symptoms (hypersalivation, emesis) resolved within 24 hours.

Chronic toxicity, Reproductive toxicity, Tumorigenic potential

No studies were performed due to the identity of rsCT with ssCT and established safety of ssCT from the literature data.

Mutagenic potential

Sufficient in vitro mutagenicity testing has been conducted. As expected, no relevant indications for mutagenic activity were observed.

Local tolerance

Studies investigated local tolerance after single intra-arterial, paravenous, intravenous, or intramuscular injection to rabbits or rats, respectively. Altogether, rsCT was well tolerated. If any, it produced only slight and reversible irritation, similar or less than that produced by the vehicle or comparator control.

Special toxicity studies - immunogenicity

As observed with conventional sCT, rsCT was not immunogenic in a short-term repeated-dose experiment in rats. Circulating antibodies against calcitonin could not be detected.

Reproductive toxicology

An issue pertaining to calcitonin preparations in general was discussed. On the basis of reproductive toxicology studies in rats and rabbits performed more than 20 years ago, no foetal abnormalities would be anticipated following the administration of Forcaltonin during pregnancy. They showed a reduction in foetal weight, or possibly the development of maternal renal tubule dilation and hyaline cast formation, particularly at doses corresponding to approximately 53 times the intended therapeutic dose or higher. The consequences on the use of sCT in pregnancy are discussed in the relevant section.

Carcinogenicity

A second issue pertaining to calcitonin preparations in general was also discussed. Several investigators observed a higher incidence of pituitary tumors in rats treated with high doses of calcitonin for approximately one year. In repeated dose studies in mice and dogs using calcitonins, no indication of enhanced pituitary proliferation could be found. This speaks in favour of a species-specific tumour-promoting effect of sCT only in rats. The extensive clinical experience with sCT without any noted increased incidence of pituitary tumours indicates that this tumour-promoting effect does not extend to man. Patients with MTC (medullary thyroid carcinoma), who are exposed to extremely high levels of endogenous calcitonin, also show no increased incidence of pituitary lesions. This evidence supports the position that the tumours observed in rats are species-specific and have no clinical relevance.

Summary and conclusion on preclinical pharmacology and toxicology

In an adjusted pharmacological-toxicological testing programme involving predominantly single dose studies, rsCT did not show any effects, which may prohibit clinical use. The batches of rsCT showed equivalence to batches of conventional sCT concerning pharmacodynamic and pharmacokinetic characteristics as well as tolerance.

These data are accepted on the basis that authenticity and purity of rsCT has been proven. Therefore, from a pharmaco-toxicological view, all preclinical pharmacology and toxicology issues are considered to be adequately resolved.

4. Clinical aspects

Forcaltonin is intended for the treatment of: Paget´s disease and hypercalcaemia of malignancy.

Three double-blind controlled clinical studies (comparator: ssCT) were submitted (U1PC-1, U1PC-2, U1PC-3) with the primary objective to prove superimposable pharmacokinetic and pharmacodynamic

responses. The three studies had also the secondary objective to assess and compare the safety and tolerability of Forcaltonin with a marketed synthetic salmon calcitonin.

Efficacy and safety of calcitonin, including the pharmacodynamic and pharmacokinetic properties of exogenously administered calcitonin, are described in the clinical part of the application and further supported by detailed data from relevant published literature on the clinical use of calcitonin.

Human pharmacology

The submitted clinical studies are well planned and conducted in accordance with the applicants SOPs, USA GCP ant the European Good Clinical Practice for Trials on Medicinal Products and under the Declaration of Helsinki Principles.

Pharmacodynamics

Study U1PC-1 (Single centre, Single-Dose, double-blind, randomised, crossover comparative pharmacodinamic study of 100 IU Forcaltonin and 100 IU of a marketed synthetic salmon calcitonin in 36 healthy normal female volunteers).

This study has been designed to compare pharmacodynamics and demonstrate superimposable response to a licensed synthetic salmon calcitonin, as judged by the responses of plasma cAMP and serum calcium.

Parenteral administration of sCT is followed by a rapid rise in plasma cAMP concentration. The response of plasma cAMP to calcitonin is thought to be a receptor-mediated activation of the adenylate cyclase-cAMP system at skeletal site; in addition calcitonin has an acute effect on renal function, provoking increases in cAMP excretion.

The primary mechanisms of the calcium lowering effect of calcitonin have been shown to be a decrease in osteoclast mediated bone resorption and the inhibition of tubular reabsorption of calcium resulting in an increased calcium excretion.

Healthy female volunteers, aged between 18 and 40 years received a single, subcutaneous 100 IU dose of either Forcaltonin or ssCT. Blood samples were collected for determination of plasma cAMP and total serum calcium.

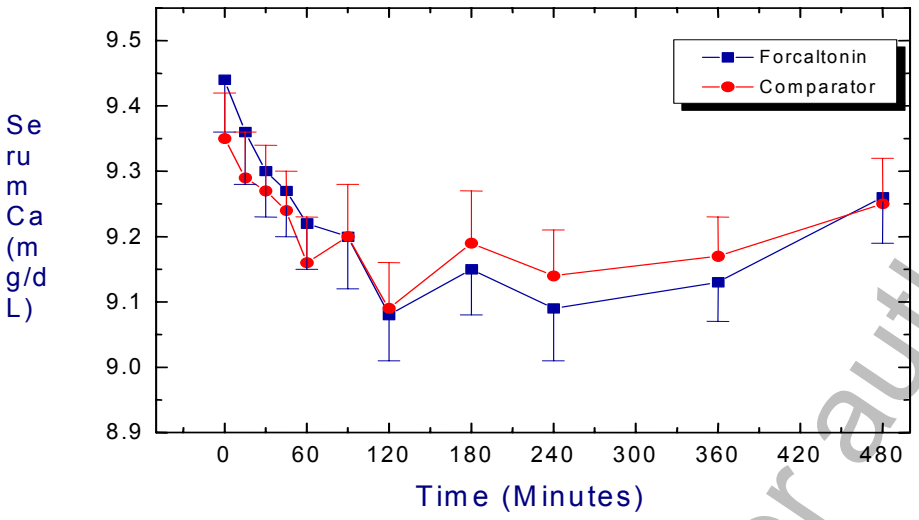
Following a washout period of 7 days, subjects received the alternate test material.

All data were analysed using an analysis of variance. All computations were performed using the Statistical Analysis System (SAS).

After injection of Forcaltonin or a marketed ssCT a substantial increase in cAMP is seen . No statistically significant differences were found between treatment groups.

A serum calcium lowering effect was observed after Forcaltonin or a marketed ssCT injection. A statistically significant greater response was found with Forcaltonin, but was not judged clinically relevant.

Figure 1: Mean Serum Calcium Levels Following 100 IU Injection of Forcaltonin [rsCT] or Comparator [ssCT] in Normal Female Volunteers (Study U1PC-1)



Study U1PC-2 and Study U1PC-3: Multi-Dose, Double-Blind, Crossover Study of 100 IU of Forcaltonin and 100 IU of a marketed synthetic salmon calcitonin in female osteoporotic subjects (30 patients were enrolled in Study U1PC-2 and 28 patients in Study U1PC-3).

One objective of these studies was to compare Forcaltonin and a marketed synthetic salmon calcitonin in their response to bone resorption parameters. Response was measured as changes in urinary concentration of deoxypyridinoline and the C-terminal type I collagen telopeptide following drug administration.

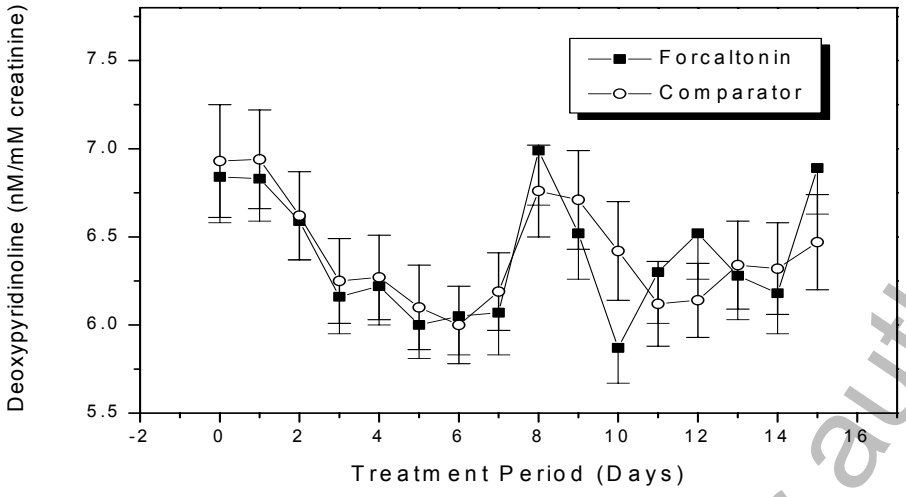
Urinary excretion of deoxypyridinoline decreased significantly following exposure to calcitonin and increased to baseline after withdrawal. There was no difference in response between Forcaltonin and ssCT.

With respect to urinary excretion of collagen C-terminal peptide, the results showed a marked decrease of urinary excretion at the start of exposure with an increase to baseline at the end of the five day treatment.

There was no statistically significant difference between the response obtained with Forcaltonin or ssCT.

The changes in biochemical markers of bone resorption induced by calcitonin shown in these two independent trials were consistent with results of published studies. Forcaltonin and ssCT showed both a rapid decrease in deoxypyridinoline and collagen C-terminal peptide levels . In addition, the test preparation and the approved synthetic salmon calcitonin were almost identical in plasma cAMP response and in their calcium lowering effect. Thus, pharmacodynamic equivalence of the recombinant preparation Forcaltonin and ssCT can be confirmed.

Figure 2: Mean Urinary Deoxypyridinoline Levels Following 100 IU Injection of Forcaltonin [rsCT] or Comparator [ssCT] in Postmenopausal Osteoporotic Women (studies U1PC-2 and 3)

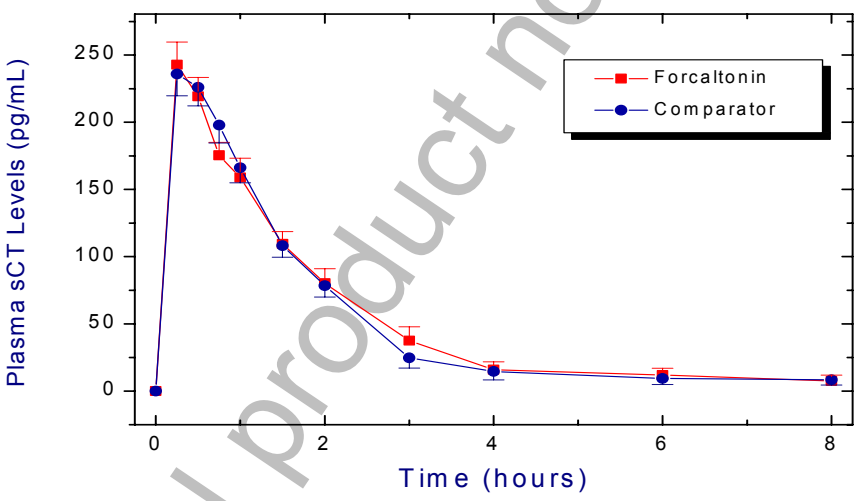


Pharmacokinetics

A primary objective of the U1PC-1 study was to measure plasma salmon calcitonin levels. The pharmacokinetic profiles of Forcaltonin and ssCT are nearly superimposable: there was no difference between Forcaltonin and ssCT as judged by AUC, Cmax or tmax. The 90% confidence intervals for AUC and Cmax were contained within the boundaries required for bioequivalence. The values for Tmax were also comparable.

The results of the study support the bioequivalence of Forcaltonin and ssCT.

Figure 3: Mean Plasma sCT Levels Following 100 IU Injection of Forcaltonin [rsCT] or Comparator [ssCT] in Normal Female Volunteers (study: U1PC-1)



Therapeutic indications

Evidence of the efficacy of ssCT in the approved indications has been available for an extensive period of time and the evidence of the clinical efficacy of Forcaltonin is derived from the data reported in the scientific literature on synthetic salmon calcitonin.

A summary of the literature data in support of the dosage regimens in the approved indications, is presented below:

Paget´s Disease

Effective doses of sCT in Paget´s disease vary from 50 IU on alternate days to 100 or 200 IU daily The minimum effective dose is 50 IU on alternate days or thrice weekly. More complete responses are seen with 100 IU thrice weekly or daily administration of 50 - 100 IU.

The recommended dose is 100 IU per day, which lies within the range in current clinical use in the EU member states.

The applicant also mentions that doses of 50 IU thrice weekly have achieved clinical and biochemical improvement and that the dosage of Forcaltonin should be related to the severity of the disease.

The thrice-weekly dosage is also in line with the current clinical practice.

Duration of treatment varies from 3 to 18 months, sometimes it is stated that treatment can be continued for a longer period if necessary.

No recommendation of treatment duration is given, as the applicant outlines that treatment may be monitored by measurement of suitable markers of bone resorption such as alkaline phosphatase or urinary hydroxyproline or deoxypyridinoline.

However, monitoring by deoxypyridinoline appears to be not yet suitable for clinical routine.

Therefore the SPC states that treatment duration will depend on the response and clinical indications for treatment.

Hypercalcaemia of malignancy

The fall in serum calcium following administration of sCT is rapid and occurs within 2 hours. The decrease in calcium is approximately 0.5 mmol/L. There is also evidence that intravenous infusion rather than a bolus injection gives a more complete response. The maximum response is observed after approximately 2 days; the duration of response persists for 7-14 days, and may wane thereafter, perhaps due to a loss of effect on bone. The effect of sCT to decrease renal tubular reabsorption of calcium may persist much longer.

The optimal dose of calcitonin to induce serum calcium decrease is unknown. There is no apparent difference in efficacy between doses in the range from 100-400 IU daily. Most of the clinical experience has been with the higher doses - up to 10 IU/kg body weight every 6 hours, 400 IU 8 hourly , 8 IU/kg 6 hourly.

A starting dose of 400 IU every 6 to 8 hours by subcutaneous or intramuscular injection in addition to intravascular volume repletion is recommended.

If the response is not satisfactory after one or two days, the dose may be increased to 10 IU/kg body weight every 6 to 8 hours. In severe or emergency cases, intravenous infusion with 10 IU/kg body weight in 500 ml physiologic saline may be administered over a period of at least 6 hours.

As a dose of 10 IU/kg body weight every six hours lies outside the range given in most member states the CPMP recommends to modify the dose to 10 IU/kg/day

Safety

Safety and tolerability of Forcaltonin and ssCT were assessed and compared in the U1PC-2 and U1PC-3 studies, already described in the pharmacodynamics and pharmacokinetics section of this report. Safety data of U1PC-1 study are also included.

The three studies evaluated tolerability and safety as secondary endpoints by assessing the adverse events including injection site inspection, evaluation of clinical laboratory data, physical exam/vital sign assessments and ECG findings, and the evaluation of orthostatic hypotension effect.

Analysis of adverse events included Fisher´s exact test and McNemar´s test. Vital signs and laboratory data were analysed using an analysis of variance.

The spectrum of side effects, which occurred in these studies, is not different from the side effects known from published studies.

The most frequent side effect reported in publications is nausea followed by facial flushing, local pain at the injection site, diarrhoea, and vomiting. Less frequent side effects are headache, metallic taste in the mouth, urticaria at the site of injection and polyuria. Generalised urticaria and tremor have been reported but are exceptionally rare.

In summary, there were no relevant differences in side effect profile and incidences between Forcaltonin and ssCT.

Adverse events

Neither serious adverse events nor deaths occurred in the studies performed.

The most common AEs were nausea ear flushing, facial flushing and vomiting. There were no statistically significant differences between groups in the incidence of nausea, which occurred in more than half of the patients, or vomiting (around 30% of the patients). The higher incidence of nausea and vomiting in the U1PC-1 study was not unexpected in a healthy volunteer population receiving a therapeutic dose of calcitonin for the first time.

Other observed AEs were diarrhoea and increased urinary frequency.

In study U1PC-2, statistically significant differences between the groups were found for the patients with facial flushing and increase in urinary frequency (21.4% in the Fortical group, 3.6 % in the comparator. In study U1PC-3, the percentage of patients with headache was significantly higher in the Forcaltonin group (32.1% against 12.5%).

Evaluation of injection sites

The site of injection was inspected and evaluated for any sign of erythema, ecchymosis, swelling, tenderness or persistence of pain and warmth following the injection and at different times post-injection.

Very few abnormal findings were observed and no statistically significant treatment group difference was found. There were no statistically significant differences between the treatment groups at any time-point.

Clinical laboratory evaluation

Standard clinical laboratory tests were made during the study visits.

There were some laboratory parameters (AST, GGTP, total protein, bilirubin and basophil percentage, cholesterol, sodium, creatinine, uric acid, albumin and urine pH) with mean changes from screening values which were statistically significant but since all changes were within the reference range, none of them was clinically relevant.

Vital signs and ECG

Systolic blood pressure, diastolic blood pressure and pulse, each in both the supine and standing position had been monitored. There were no clinically significant differences between groups for vital signs, nor clinically relevant ECG abnormalities were observed.

Orthostatic hypotension

Few events of orthostatic hypotension occurred(three patients had a total of five orthostatic episodes post-injection: 1 following Forcaltionin, 4 after comparator). None of the episodes of orthostatic hypotension was symptomatic. No significant differences between the treatment groups were found.

Use in pregnancy

There is some experience providing data against a strict withholding of sCT in pregnancy. However, the current SPC labelling with respect to use during pregnancy and lactation is in accordance with the accepted opinion that calcitonin may be used if considered essential.

Taking together the results of these three studies, it can be concluded that both drugs were safe and well tolerated in these studies. Between groups there were no significant differences in the overall incidence of adverse events, incidence by severity or incidence by relationship to test drug, in the incidence of nausea, vomiting, injection site reaction, or categorical shifts of clinical laboratory findings, except for facial flushing and urinary frequency in the U1PC-2 study and the incidence of headache in the U1PC-3 study.

5. Overall conclusions and benefit/risk assessment

Forcaltonin recombinant salmon calcitonin has been demonstrated to have the authentic molecular, biological and pharmacological properties of chemically synthesized salmon calcitonin.

Pharmacodynamic properties of Forcaltonin were compared to a marketed synthetic salmon calcitonin in healthy volunteers and patients. Superimposable response of plasma cAMP and serum calcium to a single injection of Forcaltonin or ssCT could be demonstrated in healthy volunteers. The measurement of two urinary indices of bone resorption, deoxypyridinoline and the C-terminal type I collagen telopeptide demonstrated an almost identical response of Forcaltonin and ssCT in two independent studies.

Bioequivalence of Forcaltonin and ssCT was also demonstrated in a single dose study with healthy volunteers. The pharmacokinetic profiles of Forcaltonin and ssCT are nearly superimposable, the 90% confidence interval for AUC and Cmax were contained within the boundaries required for bioequivalence and the values for Tmax were comparable.

On the basis of the demonstrated authenticity of rsCT with respect to ssCT, and the demonstrated identicality of Forcaltonin and medicinal products containing ssCT, evidence of the clinical efficacy of Forcaltonin in the indications: Paget's disease of the bone and hypercalcaemia of malignancy, as derived from the literature on synthetic salmon calcitonin, was considered acceptable.

Three studies were performed to assess safety and tolerability of Forcaltonin compared to ssCT. The side effect profile of Forcaltonin was not different from that of ssCT. No clinically relevant treatment group differences were found.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Forcaltonin was favourable in the treatment of Paget's disease and hypercalcaemia of malignancy.