Annex II

Scientific conclusions and grounds for

variation to the terms of the marketing authorisations of the injectable formulations of calcitonin

and

suspension of the marketing authorisations of the intranasal formulations of calcitonin

Scientific conclusions

Overall summary of the scientific evaluation of calcitonin-containing medicinal products (see Annex I)

Calcitonin is a hypocalcaemic compound secreted from the thyroid. Its hypocalcaemic properties are mediated primarily through the inhibition of osteoclast-mediated bone resorption.

Parenteral formulations of calcitonin were first licensed in Europe in 1973. Since 1987 calcitonin has also been available as an intranasal formulation. Calcitonin is currently authorised in most European member states.

Injectable calcitonin is available as a solution for injection or infusion at 50, 100 or 200 International Units (IU)/ml. One IU corresponds to approximately 0.2µg of synthetic salmon calcitonin. The product can be administered intramuscularly, subcutaneously or intravenously. The intranasal formulation is available at 100 or 200 International Units (IU)/ml.

More recently a new oral formulation for calcitonin has been developed which consists of the peptide hormone and 5-CNAC (8-(N-2-hydroxy-5-chloro-benzoyl)-amino-carpylic acid), a newly developed enhancer of gastrointestinal peptide absorption. This new oral formulation has not been submitted for approval in any of the EU member states.

Concerns on the efficacy of certain indications were previously raised, which resulted in a referral under Article 12 of Directive 75/319/EC (corresponding to Article 31 of Directive 2001/83/EC) in 2000. After review of the available data, the CHMP (previously CPMP) adopted an opinion on 21 November 2002, on a favourable benefit/risk balance of injectable calcitonin in the following indications:

- the prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures
- Paget's disease
- hypercalcaemia of malignancy

For intranasal calcitonin, the benefit risk balance was considered favourable only in:

- the treatment of established postmenopausal osteoporosis in order to reduce the risk of vertebral fractures. A reduction in hip fractures has not been demonstrated.

A Commission Decision for this previous referral procedure was issued on 12 June 2003.

Concerns of a possible association between calcitonin and prostate cancer have been raised and considered at different times. However, review of available data at the time by National Competent Authorities did not indicate a causal relationship. The issue was however kept under close monitoring.

In November 2010, preliminary safety findings relating to prostate cancer were observed during two clinical trials for the new oral formulation of calcitonin. On the basis of this new safety information the UK requested the opinion of the Committee for Medicinal Products for Human Use (CHMP), under Article 31 of Directive 2001/83/EC whether the marketing authorisations for medicinal products containing calcitonin should be maintained, varied, suspended or withdrawn.

The CHMP reviewed the currently available short and long-term evidence of efficacy of calcitonin in the authorised indications (as per Commission Decision of 12 June 2003), and the information about the risk of cancer with calcitonin from pre-clinical studies, clinical trials, post-marketing spontaneous reports, pharmacoepidemiological studies and published literature. The CHMP also considered information provided by third parties during the referral procedure.

- **Efficacy**

The indications currently authorised as per the outcome of the previous referral procedure that was concluded in 2003, were reviewed in the current procedure.

In addition to the published literature in relation to the use of injectable calcitonin for hypercalcaemia in malignancy, this indication is further supported by its established use in clinical practice.

With regards to the use of injectable calcitonin in acute bone loss prevention, the evidence of efficacy is based on published literature. The CHMP accepted that some evidence of efficacy in this indication has been provided, mainly by the study by Tsakalakos *et al*.

For Paget's disease, the evidence of efficacy is based on published literature of a number of small studies, where the treatment duration was in most cases between 3-18 months. Based on these data, the CHMP confirmed the benefits of injectable calcitonin in the short term treatment of the Paget's disease.

The indication of fracture prevention in osteoporosis, is supported by results from a reasonably sized, placebo controlled double blind study known as the PROOF (Prevent Recurrence of Osteoporotic Fractures) study. This pivotal study showed that only one of the investigated doses - 200IU calcitonin/day was associated with a statistical significant effect, although for this dose, statistical significance was not achieved when analysing patients with at least 2 new vertebral fractures. In addition to the lack of a dose response, the results of this study are further limited by important methodological limitations (lack of adjustment for multiple testing and very high percentage of patients discontinuing the study). Even when overlooking these limitations, the overall clinical benefit of calcitonin in osteoporosis appears to be very modest, with an absolute reduction of approximately 6% and 1.7% in the patients with ≥1 and ≥2 new vertebral fracture respectively compared to patients treated with placebo.

- **Safety**

During this procedure the CHMP reviewed the available evidence on the risk of cancer with the use of calcitonin.

The results of the biggest of the trials conducted with intra-nasal calcitonin , study CT320 (also known as the PROOF study), provides some evidence of an increased risk of cancer in the calcitonin arm compared with placebo even though the reported results fail to reach statistical significance (relative risk, 95%CI: 1.47 (0.91-2.36)).

Further evidence of a possible association between calcitonin and the risk of cancer is provided by a meta-analysis of 17 randomised, controlled, double blind studies with intranasal calcitonin performed by one of the MAHs. The Odds Ratio (OR) for the incidence of cancer in these trials in patients treated with calcitonin was 1.61 (1.11-2.34). When including trials in which no cases of malignancy had been reported the estimated OR is 2.12. The increase in absolute risk of cancer for patients treated with calcitonin compared with placebo in the intra-nasal trials was 2.36%. The most commonly reported malignancies in these trials were basal cell carcinoma and breast cancer.

In addition, the mortality analysis revealed that only patients treated with calcitonin died from cancer during these trials, which suggests that calcitonin accelerates tumour growth.

Further evidence of a positive association between calcitonin and cancer was provided from the analysis of recently conducted trials with the new oral calcitonin formulation. Two of these were

osteoarthritis studies (C2301 and C2302), where patients received 0.8mg twice daily. The third one was study A2303, a phase III study with the new oral calcitonin formulation, conducted in post-menopausal women with osteoporosis.

In the first of these trials (study C2301), a statistical significant increased risk of cancer was reported in patients treated with calcitonin compared with placebo (incidence rate ratio 4.13 (1.67-10.19)). The most commonly reported malignancy in this study was prostate cancer. As a result, an intensive post-hoc prostate cancer screening programme was implemented for all male participants in the two osteoarthritis trials. The increased risk of cancer with calcitonin in the other two trials with the new oral formulation, was not statistically significant incidence rate ratio of 1.61 (0.81-3.16) and 1.10 (0.82-1.48) for studies C2302 and A2303 respectively. Possible explanations for these discrepant results include the lower dose in the osteoporosis trial, and the premature discontinuation of male patients and an intensive prostate cancer screening programme in the second osteoarthritis trial, which identified additional cases and may have masked possible imbalances of cancer cases across the different treatment arms in these trials. However, in all trials there was a higher incidence of malignancies reported in calcitonin treated patients compared to placebo. In addition, the meta-analysis of the trials with the new formulation showed a statistical significant increase in the incidence rate ratio for patients treated with calcitonin, 1.33 (1.035-1.72), similar to the increase observed during the intranasal trials. Importantly, cancer mortality was again considerably higher in calcitonin treated patients in these trials compared to placebo; 7 cases (37.5%) compared to 2 (10.5%).

With regards to prostate cancer, information provided on prostate specific antigen (PSA) levels from all male patients in the first two osteoarthritis studies C2301 and C2302 showed that calcitonin does not have an effect on PSA levels. However the PSA analysis alone is of limited value as it is known that factors other than prostate cancer can influence PSA values and cannot explain the higher incidence of prostate cancer in patients treated with calcitonin. A number of published studies using prostate cancer cell lines and animal models have also suggested a role for calcitonin in prostate cancer progression. Although these studies in isolation were considered so far insufficient to establish a causal association due to some important limitations and the lack of any robust evidence of risk in humans, they assume a new significance in light of the more recent data from the calcitonin clinical trials.

Data from the Sanofi-Aventis pharmacovigilance database and the Novartis Global Safety Database were also analysed to identify all cases mapping to the Neoplasms benign, malignant and unspecified system organ class (SOC). Bearing in mind that the majority of the cases are very sparsely documented, establishing causality for an adverse event such as cancer based solely on spontaneous reports is not feasible.

The consistency of the results in the oral and intranasal trials suggests that the reported events are causally associated with calcitonin. The majority of the cancer cases reported in the calcitonin trials occurred after 12 months of treatment. A possible explanation, for the relatively short time of onset is that calcitonin promotes tumour progression rather than oncogenesis, as has also been suggested in the published literature addressing the role of calcitonin in prostate cancer. However despite the likelihood that calcitonin is involved in cancer promotion the exact mechanism that could explain the increased occurrence of malignancies in calcitonin treated patients has not been fully elucidated.

The diminishing use of calcitonin over the last years suggest that there is limited scope to further investigate the association by means of epidemiological studies, which in any case would be difficult to conduct and adequately control for all possible confounders for cancer.

Overall there appears to be sufficient and consistent evidence from the intranasal and oral calcitonin trials, that calcitonin is associated with an increased risk of cancer. This is most likely due to tumour growth acceleration, which has also been suggested in the published literature.

Overall conclusion

- Treatment of osteoporosis in order to reduce the risk of vertebral fractures (intranasal formulation)

The limited efficacy data in this indication need to be balanced against an increased risk of cancer as demonstrated in the analysis of calcitonin trials. The consistency of the evidence across clinical trial data, provide strong evidence of a causal association. Even though there is some uncertainty surrounding the true magnitude of this risk which appears to be different across the different trials the relative risk is consistently higher in patients treated with calcitonin compared with placebo.

Considering the limited evidence of efficacy, the risk of cancer associated with the use of calcitonin, and the long term duration of treatment required for this indication, the benefit risk balance for the intranasal formulation of calcitonin for the treatment of osteoporosis in order to reduce the risk of vertebral fractures, which is the only indication for this pharmaceutical form, is considered to be negative.

- Treatment of Paget's disease (injectable formulation)

As discussed previously the efficacy of calcitonin in the treatment of Paget's disease is limited and is partially validated by its well known use and its pharmacological plausibility.

In view of the safety concerns the CHMP was of the view that it was necessary to restrict the target population for this indication. Considering the availability of alternative treatments in this indication, the CHMP agreed that the use of calcitonin in Paget's disease should be limited to 3 months, and only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment. In exceptional circumstances eg. in patients with impending pathologic fracture, the CHMP agreed that the treatment duration may be extended up to a recommended maximum of 6 months. It was also agreed that periodic re-treatment may be considered in these patients taking into account the potential benefits and the association of cancer with long term calcitonin use.

- Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures (injectable formulation)

Only limited evidence of efficacy in this indication is available. However, the short-term nature of the intended use of calcitonin in these patients is expected to minimise the potential risk of cancer, and therefore the benefit/risk balance is considered to be positive, but the treatment duration should be limited. Treatment duration is recommended to be 2 weeks and not exceeding 4 weeks in any case.

- Treatment of hypercalcaemia of malignancy (injectable formulation)

Efficacy of calcitonin for this indication is supported by established use of calcitonin in clinical practice. Considering the nature of the indication in the setting of advanced cancer, the benefit/risk balance in this indication is considered still to be positive.

Risk Minimisation Measures

In order to maintain a positive benefit/risk balance for the indications of injectable formulation of calcitonin-containing products, the CHMP recommended changes to the Product Information, mainly in relation to the risk of cancer.

The CHMP also endorsed a communication i.e. Dear Healthcare Professional Communication (DHPC), to communicate the outcome of the present review.

Benefit–risk balance

The Committee concluded that the benefit-risk balance of calcitonin-containing injectable formulations indicated in the treatment of Paget's disease, hypercalcaemia of malignancy and for the prevention of acute bone loss due to sudden immobilisation, remains positive under normal conditions of use, subject to the restrictions in indication (for Paget's disease), limitation of treatment duration and warnings to be introduced in the product information.

The Committee also concluded that the benefit-risk balance of calcitonin-containing intranasal formulation indicated for the treatment of osteoporosis is no longer positive under normal conditions of use and recommends the suspension of the corresponding marketing authorisations.

For the lifting of the suspension the MAH(s) should provide new randomised controlled data that will be able to robustly demonstrate that the benefits of calcitonin-containing medicines outweigh their risks in patients with osteoporosis and taking into account the increased risk of cancer and cancer mortality associated with long term use of calcitonin.

Re-examination procedure

Following the adoption of the CHMP opinion and recommendations during the July 2012 CHMP meeting, a re-examination request was received on 8 August 2012 from one of the MAHs Therapicon, who was involved in the referral procedure. Grounds for re-examination were received on 22 September 2012. The re-examination of the CHMP opinion was related to the benefit-risk balance of the intranasal formulation of calcitonin in the *indication "treatment of osteoporosis in order to reduce the risk of vertebral fractures".*

The scientific points of disagreement presented in the MAHs detailed grounds included efficacy aspects, safety aspects in relation to the risk of cancer (non-clinical, pharmacovigilance, and statistical issues) and overall benefit-risk assessment. The CHMP conclusions in response to these points raised by the MAH are given below.

The CHMP also consulted a group of experts on 6 November 2012 to gain their view on a number issues.

- Efficacy aspects

The CHMP agrees that the PROOF study provides support for the efficacy with regard to vertebral fracture rates in the 200 IU dose group corresponding to a p-value of 0.032 and with no statistically significant changes in the lower (100 IU) and higher (400 IU) dose groups. However, as previously concluded by CHMP there are concerns in relation to the lack of a dose response in this study as well as in relation to other methodological limitations.

The MAH argued that the improvement in bone mineral density (BMD) underestimates fracture efficacy. The CHMP considered that BMD, is still regarded to be an important surrogate marker, which was shown to have a modest but statistically significant increase in comparison with placebo.

- Safety aspects

The MAH addressed a number of non-clinical, pharmacovigilance, and statistical issues in relation to the CHMP assessment of the risk of cancer with the use of calcitonin-containing medicinal products.

Non-clinical aspects

The CHMP is of the view that it is not possible to reach a conclusion about the association between calcitonin and cancer progression from the results of the published non-clinical in vitro studies. Data suggest that there is some relation for prostate cancer but it is not possible to generalise these results.

The most relevant non-clinical studies are the chronic carcinogenicity assays in rats and mice and they are not conclusive with regard to the carcinogenic potential of calcitonin.

Statistical issues (meta-analysis)

The MAH also raised some points on the methodological flaws of the meta-analysis of the 17 intranasal calcitonin studies and provided a re-analysis of data. The MAH argues that the studies included in the meta-analysis lacked a defined PICO (population, intervention, comparison and outcome) statement. The CHMP noted that any meta-analysis driven by a safety signal will always be, per definition, conducted post-hoc, the objective of such an analysis being to quantitatively rule out a potential harm to patients. For this purpose the methodology used was judged to be sufficient by the CHMP.

The MAH also questions the validity of the evidence of the available clinical trials that substantiated the efficacy of the product, arguing that the evidence is not valid for safety because of confounding factors. While this argument might be valid for observational studies, the CHMP is of the view that potential bias in randomised clinical trials that could favour one of the treatment arms is unlikely, as the randomisation procedure provides sufficiently well balanced groups. Even so, the CHMP concluded that there is evidence of an increased risk of cancer among the exposed, with some degree of consistency – especially among the larger studies.

The MAH considers that the exclusion of four studies from the meta-analysis in which no cancer cases were observed, lacks basis. While it is recognised by the CHMP that the inclusion or exclusion of single trials will adjust the overall odds ratio (OR) in different directions, it is acknowledged that it is reasonable to conduct a list of sensitivity analyses to assess the robustness of the results. The differences are not considered to be sufficiently convincing to alter the previous CHMP conclusion regarding an increased risk of cancer with calcitonin-containing medicinal products.

The MAH questions the results of the meta-analysis because of the use of fixed-effects models in the presence of heterogeneity. The CHMP considers that while this argument might be valid for the meta-analysis conducted on the studies with the oral formulations, it cannot be supported in the analysis with all intranasal trials where no clear heterogeneity is observed. Moreover, beyond any discussion of whether the statistical significance is achieved in some cases or not, there is an evident, consistent and clear trend of an increased risk of cancer. In this setting, the statistical significance is superseded by clinical relevance.

It is also pointed out by the MAH that the point estimate OR is used, which is more likely to provide a significant result than the corresponding RR. However the CHMP was of the view that regardless of whether OR or RR are used, the signal is apparent, which can even be partly assessed by even looking at crude rates. The inconsistency in the summary statistics given is recognised by the CHMP but the impact on the overall interpretation must be regarded as marginal or non-existing.

The MAH also discusses the lack of causality based on the Bradford-Hill criteria, which have been taken into account and assessed. However none of the arguments presented refute the conclusion derived from the results of the intranasal (and oral) studies, which suggests that that there is an increased risk of cancer associated with the use of calcitonin.

Pharmacovigilance

The MAH discussed the low number of post-marketing spontaneous cases of cancer reported with calcitonin. The CHMP noted that the low reporting is not unexpected in this particular situation where the event under scrutiny (i.e malignancies), is not uncommon in the target population that otherwise receive a number of concomitant medications, where the risk increases with time making it very unlikely for physicians to establish a possible relation. Another factor that could explain low reporting rate is the fact that calcitonin have been authorised for nearly 40 years. Therefore, the scarce number

of cases of cancer in patients who are or have been treated with calcitonin that are found in global safety databases cannot lead to any conclusions, mainly when balanced against data coming from clinical trials.

- Overall benefit-risk assessment

As mentioned before, it is agreed that the PROOF study shows a modest efficacy of calcitonin in the reduction of the risk of vertebral fractures. However, the new evidence related to the risk of cancer impacts the safety profile of calcitonin-containing medicines.

From the meta-analysis of the intranasal calcitonin studies, the data point towards an increase in the risk of cancer in patients treated with intranasal calcitonin compared to placebo. As expected, the risk of cancer increases when excluding the four studies with no events. These data are also supported by the meta-analysis of the 3 studies (C2301, C2302 and A2303) performed with the oral formulations.

Recognising the potential limitations of the clinical trials included in the analysis, the observed increased risk of cancer needs to be balanced against the modest benefit of calcitonin.

Overall conclusion of the re-examination procedure

The scope of the re-examination was the benefit/risk of intranasal formulation of calcitonin-containing medicinal products in the indication of "treatment of osteoporosis in order to reduce the risk of vertebral fractures".

Based on the totality of the data available on the safety and the efficacy of intranasal calcitonin-containing medicinal products and having noted the opinion of the Ad-Hoc Expert meeting, the CHMP confirmed its initial conclusion that the limited efficacy in this indication needs to be balanced against evidence from clinical trials for an increased risk of cancer with long-term use of calcitonin.

Considering the limited evidence of efficacy, the risk of cancer with the use of calcitonin, and the long term duration of treatment required for this indication, the benefit risk balance for the intranasal formulation of calcitonin for the treatment of osteoporosis in order to reduce the risk of vertebral fractures, which is the only indication for this pharmaceutical form, is considered to be negative.

The Committee therefore concluded the benefit-risk balance of calcitonin-containing intranasal formulation indicated for the treatment of osteoporosis is no longer positive under normal conditions of use and recommends the suspension of the corresponding marketing authorisations.

For the lifting of the suspension the MAH(s) should provide new randomised controlled data that will be able to robustly demonstrate that the benefits of calcitonin-containing medicines outweigh their risks in patients with osteoporosis taking into account the increased risk of cancer and cancer mortality associated with long term use of calcitonin.

Grounds for the variation to the terms of the marketing authorisation for the injectable calcitonin-containing medicinal products

Whereas

- The Committee considered the referral made under Article 31 of Directive 2001/83/EC for calcitonin-containing medicines;
- The Committee considered all the available data on the efficacy and safety of calcitonin-containing medicines in particular new data in relation to the risk of cancer.
- The Committee is of the opinion that data from clinical studies provide evidence for an increased risk of cancer with long-term use of calcitonin.

- The Committee therefore considered the benefit-risk balance of injectable calcitonin-containing products under normal conditions of use in each of the authorised indication and concluded that:
    - for the treatment of Paget's disease the benefit-risk balance remains positive provided that the duration of use is restricted to 3 months and only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment. The duration of treatment may be extended to a maximum of 6 months under exceptional circumstances and periodic re-treatment may be considered.
    - for the prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures, the benefit-risk balance remains positive provided that the duration of use is restricted to 2 weeks, not exceeding 4 weeks in any case.
    - for the treatment of hypercalcaemia of malignancy the benefit-risk balance remains positive provided that the treatment duration is limited to the shortest possible time using the minimum effective dose
- The Committee considered that in order to maintain a positive benefit-risk for the above indications additional changes to the product information (section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects) in relation to the risk of cancer should be included.

Therefore, the Committee recommended the variation of the marketing authorisations for calcitonin containing medicinal products (injectable formulations) in accordance with changes to the product information as set out in Annex III of the CHMP Opinion.

Grounds for the suspension of the marketing authorisation for the intranasal calcitonin-containing medicinal products

Whereas

- The Committee considered the referral made under Article 31 of Directive 2001/83/EC for calcitonin-containing medicines;
- The Committee considered all the available data on the efficacy and safety of calcitonin-containing medicines in particular new data in relation to the risk of cancer.
- The Committee is of the opinion that data from clinical studies provide evidence for an increased risk of cancer with long-term use of calcitonin.
- The Committee in light of the previous review and in the absence of new efficacy data, considered that the intranasal calcitonin-containing medicines can be effective in the treatment of established postmenopausal osteoporosis in order to reduce the risk of vertebral fractures. However the evidence of efficacy of intranasal calcitonin-containing medicines in this indication remains limited.
- The Committee also took in to account that in patients with osteoporosis, intranasal calcitonin treatment is to be administered on a long-term basis.
- In view of the new safety concerns in relation to the risk of cancer in long-term use and the limited efficacy of calcitonin in the treatment of osteoporosis, the Committee is of the opinion that pursuant to Article 116 of Directive 2001/83/EC the benefit-risk balance of the intranasal formulations of calcitonin-containing medicinal products is not positive under normal conditions of use.

Therefore the Committee recommended the suspension of the Marketing Authorisations for the intranasal formulation of calcitonin.

The conditions for the lifting of the suspension of the Marketing Authorisations are set out in Annex IV of the Opinion.