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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

# CONCEPT PAPER ON THE NEED FOR AN ADDENDUM ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INTENDED FOR TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

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## 1. INTRODUCTION

Oral glucocorticoid therapy is widely used for the treatment of a variety of diseases. Approximately 1% of the population is prescribed oral glucocorticoids, and in the elderly this prevalence rises to 2.5% [1]. The association between glucocorticoid therapy and osteoporosis is well documented and exhibits some characteristic features [2]. Bone loss is particularly rapid in the first few months after initiation of therapy, with a slower rate of loss subsequently [3]. Fracture risk also increases rapidly during the early months of therapy and declines after its cessation [4,5]. Both cortical and cancellous bone are affected, and there is some reversibility of bone loss after cessation or reduction of therapy [3,6]. Although the severity of osteoporosis is related to the dose and duration of glucocorticoid therapy, some increase in fracture risk is seen even at daily doses of ≤7.5 mg daily for 3–6 months [4,5]. Finally, the effect of glucocorticoids on bone fragility is, to some extent, independent of bone mineral density, fractures occurring at a higher bone mineral density (BMD) threshold than in postmenopausal osteoporosis (PMO) [7,8,9].

Glucocorticoid-induced osteoporosis (GIOP) and PMO share a number of characteristics with respect to the cellular pathophysiology of bone loss. Increased bone turnover occurs in both conditions, but differs in its time course. In GIOP, an early and transient increase in bone turnover occurs against a background of low bone turnover with reduced bone formation at both tissue and cellular levels [10,11,12,13]. The early increase in bone turnover in GIOP is likely to be a major contributor to bone loss and increased fracture risk within the first few months of initiating therapy and is therefore an important therapeutic target. In PMO, increased bone turnover is consistently observed over time. Both GIOP and PMO are associated with a reduction in bone formation at the cellular level, this effect being quantitatively greater in GIOP than PMO and associated with a reduction in bone formation at the tissue level. Similar effects on cancellous bone microarchitecture have also been reported in the two conditions, depending on the dose of glucocorticoids used [10].

## 2. PROBLEM STATEMENT

Currently, the only guidelines dealing with osteoporosis are intended to provide guidance for the evaluation of new medicinal products in the treatment of primary osteoporosis, principally in postmenopausal women but also in men. They specifically mention that secondary osteoporosis, resulting from immobilisation, disease (hyperthyroidism, hyperparathyroidism, rheumatic arthritis) or drugs, especially glucocorticoid therapy and hormonal ablative therapies, in both genders, are not covered by this guideline [11].

## 3. DISCUSSION (ON THE PROBLEM STATEMENT)

Recommendations for the registration of agents for the prevention and treatment of GIOP were produced by the Group for the Respect of Ethics and Excellence in Science (GREES) in 1996 [12] and subsequently updated in 2005 [13]. The 2005 update mainly addressed the design of clinical studies in glucocorticoid-treated postmenopausal women and concluded that for agents with proven efficacy in PMO a placebo-controlled trial with lumbar spine BMD at 1 year as the primary endpoint was required.

A more recent update of this paper suggested considering separately appropriate recommendations for the registration of agents for use in GIOP in (i) postmenopausal women, (ii) men, and (iii) premenopausal women.

## 4. RECOMMENDATION

The efficacy working party recommends drafting an addendum on GIOP to be attached to the "Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis" (CPMP/EWP/552/95 Rev. 2).

Points to be addressed in the addendum include:

- the need for a specific preclinical package for agents already approved for PMO, or not approved for PMO;
- the need to repeat phase I and phase II studies for agents already approved for PMO;
- the need to differentiate the indications "prevention" and "treatment" of GIOP (i.e., intervention at the start of glucocorticoid therapy and intervention after at least 3 months of glucocorticoid therapy);
- the need to consider patients undergoing transplantation procedures;
- the need to separate estimation of efficacy in females and males;
- the need to separate estimation of efficacy in premenopausal and postmenopausal females;
- the need to use placebo-controlled studies with fracture as a primary endpoint or to use bone mineral density, or even other biochemical endpoints, as an acceptable surrogate endpoint;
- the expected duration of the studies.

## 5. PROPOSED TIMETABLE

The draft addendum is expected to be released for 6 months consultation in 3rd/4th quarter 2010.

## 6. RESOURCE REQUIREMENTS FOR PREPARATION

EWP is proposed to be involved. Discussions would be held during the usual EWP meetings which are held approximately every 3 months. It is anticipated that SWP (Safety Working Party) will be consulted.

## 7. IMPACT ASSESSMENT (ANTICIPATED)

It is expected that the number of products developed with the intention to treat GIOP will increase in the near future. Therefore this addendum will clarify and harmonise the requirements of the CHMP in this regard, which is of benefit to industry and assessors.

## 8. INTERESTED PARTIES

- International Osteoporosis Foundation;
- The Group for the Respect of Ethics and Excellence in Science;
- European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis.

## 9. REFERENCES TO LITERATURE, GUIDELINES ETC


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