1. Introduction. Osteoporosis induced by corticoids

The adverse effects of glucocorticoids (GC) on the skeleton have been known since Cushing’s description in 1932, who observed the decalcification which accompanied suprarenal hyperplasia due to a hypophysary adenoma which produces adrenocorticotropic hormone. The wide use nowadays of these drugs has made osteoporosis induced by glucocorticoids (OIC) the most frequent cause of osteoporosis associated with drugs, constituting, therefore, a health problem of great magnitude. So, for example, it has been estimated that 0.5% of the general population, and 1.7% of women over 55 years receive oral steroids. This means, paradoxically, that, given that we now have the necessary means for the diagnosis and prevention of OIC, fewer than 14% of patients according to some series, and 7% according to others, receive any type of treatment to avoid the loss of bone mass when they are prescribed GC orally. The recognition of this problem and early action are fundamental, given the deleterious consequences of the GCs on bone.

A study carried out in Great Britain in 65,786 outpatients showed a prevalence of the use of corticotherapy of 0.5% in the general population and 1.4% in those patients older than 55 years. The spectrum of indications for treatment with GC is very broad, but only 14% of those subjects treated, and at risk of OIC, receive active treatment for this condition.

In all the available studies, doses higher than or equal to 7.5 mg/day of prednisone produce a loss of BMD, although lower doses can drive a rapid loss of bone mass and an increase in the risk of fracture. The subjects who receive this daily dose have an increased risk of loss of BMD (which occurs mainly in the first six months), of vertebral fracture (RR= 2.86; 95% CI, 2.54-3.16) and of hip fractures (RR= 2.01; 95% CI, 1.74-2.29). The risk of fracture increases especially from the third month of treatment. There is a clear dose-depend-
ent relationship to risk of fracture. It has been established that 30-50% of subjects treated chronically with oral GCs will suffer fractures. The data available suggest a prevalence of osteoporotic fractures in subjects with OIC of, at least, double that which might have been expected.

A meta-analysis carried out by Van Staa et al. gathered all material written to date around the epidemiology of the loss of bone associated with the use of corticoids and offered a complete review of information around the risk factors for loss of bone mass and fractures. To do this, the authors gathered data from 66 studies in which were available the measurements of BMD in 2,891 patients treated with corticoids, the majority being women (71.5%) with an average age of 55.2 years. The average dose of corticoids was 9.6 mg of prednisolone (or equivalent) with an accumulative dose of 17.8 g approximately 5.4 years on average.

Among those studies collected, the one which evaluated fractures in most detail was called “General Practice Research Database” or GPRD. However, all the studies which offered information on this issue concluded that the use of corticoids increased the risk of fracture even though in those smaller studies this was not statistically significant. So, the RR of fracture in patients treated with corticoids in the GPRD study was 1.33 (95% CI 1.29-1.38) and 1.91 (95% CI 1.68-2.15) in the rest of the studies. Similarly, those patients with COPD treated with corticoids showed a higher risk of fractures than those treated for arthropathy.

It is very important to establish a relationship between the dose of corticoids administered and the incidence of fractures. The GPRD study thus indicated that the risk of fracture for patients treated with less than 5 mg of prednisolone remained stable at around 20% but that it was raised to 60% in patients on doses of 20 mg in non-vertebral fractures. In terms of the accumulative doses of corticoids, a lower correlation was found in this study, although in others this was positive and was an even stronger predictive factor than the daily dose. Looked at in detail, the GPRD study revealed an increased risk of non-vertebral fractures in 54% of patients treated with 7.5 mg or more of prednisolone daily over the first year, although therapeutic continuation at high doses did not substantially change this percentage. The interruption of therapy with corticoids reduces both the risk of developing steroidal osteoporosis as well as its complications. Thus, the GPRD study showed strong evidence of a reduction in risk of fracture in the year following the ceasing of therapy with corticoids, more evident in vertebral fractures, but also in hip fractures.

3. Physiopathology

The mechanism for the development of OIC is unknown, although it appears to be different to that of postmenopausal osteoporosis. The loss of bone mass happens, above all, in the trabecular bone, where it reaches 30% in some studies, and in the first months after the start of treatment. The most significant changes observed in OIC are a reduction in osteoblastic activity, producing a suppression of bone formation, as well as a reduction in the levels of osteocalcin, which is observed already within the first 24 hours of treatment with corticoids, and which reverts very rapidly with the cessation of the therapy, as well as the induction of osteocytic apoptosis induced by the corticoids and a reduction in the average life of the osteoclasts. It seems also that there is an increase in bone resorption, through an increase in the average life of the osteoclasts, although it is not known how much these changes reflect the action of the GCs on the bone, or are due to the underlying disease, since in other studies the results are contradictory.

Other related factors are of a hormonal type. The GCs can produce secondary hyperparathyroidism, induced by a decrease in the intestinal absorption of calcium and greater urinary elimination, or even due to the direct effect of the GCs on the glandular secretion of the parathyroid hormone (PTH). The sex steroids, which intervene in bone remodelling, can be altered by treatment with GCs, with a dose-dependent decrease in blood testosterone through an alteration in the secretion of hypothalamic hormone liberating gonadotropine, by the direct effect on the production of testosterone in the testicles, or through suprarenal suppression. They also inhibit the secretion of oestrogens stimulated by the follicle-stimulating hormone. Another mechanism which contributes to the resorptive action of the GCs is the reduction in the synthesis of osteoprotegerin. The glucocorticoids also have deleterious effects on the muscle cells, producing myopathy, with an increase in the risk of falls. Similarly, they influence the hormonal axis, reducing the production of sex hormones, including the oestrogens and testosterone, which affects the bone cells.

4. Treatment of osteoporosis induced by corticoids

4.a General non-pharmaceutical measures

Among the general measures should be considered those non-pharmaceutical measures for the prevention of fractures, which are valid both for osteoporosis in general and for secondary osteoporosis, in which OIC is included. Those patients receiving GC should follow a diet rich in calcium and protein, and carry out exercise which their underlying disease allows to maintain bone mass, since prolonged treatment with GC tends also to affect muscles, producing the aforementioned steroidal myopathy. GCs should be prescribed at the lowest dose and for the shortest period possible, since the risk of fracture increases with daily administration, with the accumulated dose and with the duration of treatment. Given that the loss of bone mass and the incidence of fractures increases rapidly after the start of treatment with GCs, therapeutic intervention should start as soon as possi-
ble, ideally from the start of the steroid therapy if it is suspected that the treatment with GC is going to last for more than 3 months.

4b. Biphosphonates

**Alendronate (ALN)**

Saag et al. carried out a study in 477 patients who were taking GC, to whom were randomly administered alendronate (ALN) at a dose of 5 mg/day or 10 mg/day, or a placebo. To another 83 patients, coming from different centres, a dose of 2.5 mg/day of ALN was administered. All the groups were given a supplement of calcium (88-1,000 mg) and vitamin D (250-500 UI). After a follow up of 48 weeks, an increase in lumbar BMD was observed in those patients taking ALN at a dose of 5 mg/day and 10 mg/day, with respect to the placebo (2.1 and 2.9% respectively), whilst the group who took 2.5 mg/day obtained only a slight increase which was not statistically significant. The increases in BMD in the femoral neck were in the order of 1% in patients who took ALN at a dose of 5 mg/day and 10 mg/day with respect to the placebo (1.2 and 1% respectively), but again, these were not statistically significant on the 2.5 mg/day group. No statistically significant reduction was seen in the risk of fractures, either vertebral or non-vertebral, in any of the groups treated with ALN. The study was extended for another year with 208 patients, who were those who completed the earlier study and who continued the corticoid treatment. The patients who had been receiving 2.5 mg/day were changed "blindly" to taking 10 mg/day of ALN, and the groups taking the placebo, ALN at 5 mg/day and ALN at 10 mg/day, were maintained (with calcium and vitamin D at the same doses). A statistically significant increase in lumbar BMD was obtained in all the groups taking ALN (2.77, 3.85 and 3.69 respectively in the groups receiving 5 mg/day, 10 mg/day and in those who had passed from 2.5 to 10 mg/day of ALN), whilst in the group that only received calcium and vitamin D it reduced by 0.8%. The differences were statistically significant. A significant reduction was also observed in the incidence of vertebral fractures in the combined group being treated with ALN, in relation to the placebo group (0.7% as opposed to 6.8%; p= 0.026), but not in the incidence of non-vertebral fractures.

**Risedronate (RIS)**

Eastell at al. carried out a study in 120 women affected by rheumatoid arthritis who were following treatment with GC, at a minimum of 2.5 mg/day for at least 6 months, with risedronate (RIS) being administered in two ways: either a daily dose of 2.5 mg, or 15 mg given cyclically (15 mg daily for 2 weeks followed by placebo for 10 weeks). The study was prolonged for 3 years, so that in the end both groups received the same quantity of RIS. At 97 weeks, in those patients who had received 2.5 mg/daily of RIS, BMD in the lumbar spine increased by 1.4%, and in the femoral neck it fell by 1.0%, while in the placebo group the fall in BMD was statistically greater (-1.6% in the lumbar spinal column and -3.6 in the femoral neck). No statistically significant differences were observed between the results of the two groups which received RIS. With respect to the incidence of vertebral fractures, which were recorded as adverse effects, the differences were not statistically significant: in the placebo group new vertebral fractures were seen in 3 of the 33 patients, in the group which received 2.5 mg/day of RIS they were observed in 7 of the 31 patients and in the group receiving 15 mg of RIS cyclically they were produced in 2 out of 30 patients.

In a co-operative multicentric study, Cohen et al. included 224 males and females who had started prolonged treatment with corticoids, carrying out a follow up over one year. In this first study of prevention it was observed that after 12 months no significant changes in BMD were produced in the spine, with either a dose of 2.5 mg or 5 mg, with respect to the baseline, although the average of the differences in BMD in the spine and femoral neck with respect to the placebo were significant (p< 0.001) and the reduction in incidental vertebral fractures which were observed in the risedronate group has no statistical significance (these were observed in 5.7% of patients receiving 5 mg daily of RIS as opposed to 17.3% in the group who had taken the placebo, p= 0.072).

The data from this study were combined with those of another study carried out with the same methodology, but directed at treatment, in which Reid et al. studied 290 patients of both sexes who had been receiving at least 7.5 mg of prednisone for 6 months. The follow up was extended for a year and an increase in BMD was observed in the lumbar spinal column (2.9%), in the femoral neck (1.8%), and in the trochanter (2.4%), as well as a reduction of 70% in vertebral fractures. Although not initially planned, the researchers in both studies decided to combine their data with the objective of obtaining a sample size which allowed them the statistical power to confirm the reduction in the incidence of fractures.

This drove the publication of a third study with a population of 518 men and women who received either placebo or RIS (in two groups: at doses of 2.5 mg and 5 mg per day, respectively), along with a supplement of 500-1,000 mg of calcium and 400 UI of vitamin D. In the joint population a statistically significant increase in BMD in the lumbar spine (1.9 ± 0.38%), in the femoral neck (1.3 ± 0.40%) and in the trochanter (2.0 ± 0.37%). In the group which took 5 mg daily of RIS the difference with respect to the placebo group at 12 months was 2.9% in the lumbar spine (p< 0.001), and 2.8% in both the femoral neck and the trochanter; p< 0.001 in both cases. With 2.5 mg of RIS daily, the increase was statistically significant only in the lumbar spine (1.3 ± 0.41%, p< 0.001). A reduction in risk of vertebral fracture was observed in both the group receiving 2.5 mg a day of RIS and in those who received 5 mg daily, since after a year of follow up new vertebral fractures appeared in
16% of those patients who took the placebo, in 7% of the group on 2.5 mg of RIS daily and in 5% of the group taking 5 mg of RIS daily. No statistically significant differences were observed in the incidence of non-vertebral fractures between any of the groups. Level of evidence 1b.

In a sub-group of 184 males from the earlier study, Reid et al.31 showed an increase in BMD with RIS at a dose of 5 mg/day of 4.8% in the lumbar spine, of 2.1% in the femoral neck, and of 2.6% in the trochanter compared with baseline values, in the treatment group (corticoids for more than 6 months). In considering in general the group of those treated with RIS as against those not treated, a reduction in risk of vertebral fracture of 82.4% (95% CI, 36.6-95.1%) was observed at the end of a year of follow up (p= 0.008).

**Zoledronate (ZOL)**
The efficacy of ZOL in steroidal osteoporosis has been studied in a non-inferiority trial19, of a year's duration, which compared the effects of ZOL, administered at a dose of 5 mg/year intravenously, with those of RIS, administered orally at a dose of 5 mg/day. The population of the study consisted of 383 women who were in treatment with 7.5 mg of prednisone. The intervention qualified as “treatment” when the women had been receiving the corticoid for more than three months, and “prevention” when they had been receiving it for a shorter time than that. The primary objective constituted the changes in BMD in the lumbar spine, and the limit of margin of non-inferiority was established at -0.70% for treatment, and at -1.12% for prevention. The secondary objectives were the changes in appendicular BMD and the incidence of vertebral fractures. All the CI points of the differences for the treatment group (limits 0.67-2.05), and for that of prevention (limits 1.04-2.88) were within the margin of non-inferiority. In fact ZOL determined increases in BMD significantly higher than RIS in the lumbar spine, both in treatment (4.06 ± 0.28% vs 2.71 ± 0.28%; p< 0.0001) and in prevention (2.60 ± 0.45% vs 0.64 ± 0.46%; p< 0.0001). They were also higher in the femoral neck (1.45 ± 0.31% vs 0.39 ± 0.30%; 1.30 ± 0.45% vs -0.03 ± 0.46%; p< 0.005 in both cases). No differences in the incidence of fractures were observed. The trial permits the recommendation of ZOL for osteoporosis due to glucocorticoids.

**4.c PTH 1-34 in the treatment of osteoporosis induced by steroids**
Up to now only studies on the fraction 1-34 of PTH (teriparatide) have been published. Lane et al.45.54 carried out a study in 49 postmenopausal women affected by chronic inflammatory diseases having corticoidal treatment (prednisone 5-20 mg/day, or equivalent for more than a year) and densitometric osteoporosis, who were randomly assigned to a control group or to a group which received treatment with teriparatide for a year. All the women received hormone replacement treatment (HRT). After a year of treatment with teriparatide the BMD in the lumbar spine, estimated by QCT (Quantitative Computed Tomography), increased by 35% compared with 1.7% (p< 0.001) in the control group, and by DXA, by 11% compared to 0% (p< 0.001) in the control group. Similarly, an increase in the transversal vertebral area was obtained of 48% (p< 0.001), while the control group showed no changes33. However, the changes in BMD in the hip and the forearm were not statistically significant. In the group treated with teriparatide there was not a single vertebral fracture, while in the control group there was one fracture.

The study was extended for one more year39, after suspending the treatment with teriparatide, and it was observed that the BMD in the lumbar spine and in the femoral neck continued to increase, which did not happen in patients who received only TSH.

Another clinical trial of 36 months, randomised, multicentric, double-blind, with active control, compared the effects of 20 μg of teriparatide daily with 10 mg alendronate daily in men and women with high risk of fracture and secondary osteoporosis due to glucocorticoids. This study included 428 men and women from 22 to 89 years of age with osteoporosis, who had received glucocorticoids at a dose equivalent to or higher than 5 mg daily of prednisone for at least 3 months. The primary objective was the evaluation of changes in BMD in the lumbar spinal column at 18 months of treatment44. The secondary objectives were the changes in BMD in total hip, femoral neck at 18, 24 and 36 months, as well as lumbar BMD at 24 and 36 months, changes in markers for remodelled bone at 18 months, incidence of fractures and safety data. At 18 months of treatment the increase in BMD in the teriparatide group was 7.2±0.7% vs 3.4%±0.7 in the alendronate group (p< 0.001), at 36 months the changes in BMD were 11.0±2.7% in the teriparatide group as against those of 5.3% in the lumbar spine, 5.2% in the total hip, and vs 3.4% in the femoral neck respectively (p< 0.001). At 6 months of treatment there were already significant differences between the two groups (p< 0.001). At 18 months of treatment the percentage of patients who experienced a new vertebral fracture in the group assigned to teriparatide was 0.6% vs 6.1% in the alendronate group (p= 0.004), at 36 months 1.7% of those receiving teriparatide had vertebral fractures compared with 7.7% of the alendronate group (p< 0.007). There were no significant differences in non-vertebral fractures. This study suggests that teriparatide possesses a higher efficacy than alendronate in the reduction of vertebral fractures as well as higher increases in the BMD of patients treated with oral glucocorticoids34. The results have also been analysed according to sex and menopausal state44. At 18 months of treatment the increases in BMD were significantly higher in the teriparatide group than in the alendronate group in postmenopausal women (7.8% vs 3% p< 0.001), premenopausal women (7.0% vs 0.7% p< 0.001) and in men (7.3% vs 3.7 p< 0.03).
5. Recommendations of the clinical guides for the prevention and treatment of osteoporosis induced by steroids

5.a Recommendations of the Working Group on Osteoporosis of the Spanish Society of Internal Medicine (GTO-SEMI)

The GTO-SEMI published in 2008 a position document on the prevention and treatment of osteoporosis induced by corticoids, after a revision of the existing bibliography, making some recommendations in accord with the available evidence, and making a separation between “who to treat” and “with what to treat” (Table 1).

Regarding “with which drug to treat”, the panel of experts considered that in all cases supplements of calcium (500-1,000 mg/day, dependent on diet) and vitamin D (800-1,000 UI/day). With respect to specific drugs, starting with the anti-resorptives, they considered that RIS and ALN are the drugs of choice, recommending that before the start of treatment with biphosphonates, the clearance of creatinine is estimated with the Cockcroft-Gault formula; when this is under 30 ml/min the dose should be reduced to 50% or the interval between doses doubled. At the time of production of the document, the results for zoledronate had not yet been published, for which reason they were not included. With respect to bone forming drugs. The committee was of the opinion that teriparatide could be indicated in especially serious cases (multiple fractures or extreme drops in BMD).

Finally, among other aspects to consider, they recommended that the treatment should be maintained while the steroidal treatment is maintained, carrying out as developmental controls an annual densitometry, as well as a lateral dorsal and lumbar spinal X-ray in all patients who have had 3 consecutive years of steroidal treatment, and if before this period of time there was a reasonable clinical suspicion of the presence of a vertebral fracture, such back pain which had recently started, or loss of stature. Finally, they recommended the use of thiazides in cases of hypercalcuria and/or coexistence of arterial hypertension.

5b. Recommendations of SEIOMM

The Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) produced some guides to clinical practice in postmenopausal glucocorticoidal, and male osteoporosis. The second edition of these was published in 2008 in the section on steroidal osteoporosis. Their conclusions were:

1) Alendronate and risedronate are efficacious in the prevention of osteoporotic fractures in patients treated with corticoids and constitute the drugs of choice (recommendation A)

2) Along with the biphosphonates, calcium and vitamin D should be administered. The active metabolites of vitamin D in themselves have a preventative action on bone loss, but there is a lack of data on the prevention of fractures.

3) The data obtained in the studies commented on earlier have resulted in the experts advising the primary prevention of osteoporosis due to GC in persons treated with 7.5 mg or more of prednisone a day (or the equivalent of another corticoid) when it is expected that this medication will be maintained for more than 3 months, and to whom one of these circumstances apply: being more than 65 years old, or having a T-score lower than -1.5 (recommendation D). The treatment should be maintained as long as the patient is receiving a dose equal to or higher than 7.5 mg/day of prednisone; it should also be maintained if the osteoporosis persists after it ceases, or if other risk factors continue (recommendation D). Given that one cannot exclude the fact that lower doses than those signalled can also provoke a reduction in BMD and fractures, above all if it is administered over a long term, in such cases the prevention or treatment can also be considered, particularly if to this other risk factors are added. In patients with normal BMD and whose intake of GC is less than 5-7 mg/day of prednisone or equivalent, some authors recommend treatment with calcium (1,200 mg/day and vitamin D 800 UI/day) only.

4) There are no studies which assess the efficacy of non-pharmacological measures, such as physical exercise, diet rich in calcium, quitting tobacco and moderation of alcohol intake, but all the guides on osteoporosis due to GC advise these measures, extrapolating the recommendations which have been given in postmenopausal osteoporosis. One should take into account the fact that the possibility of a patient carrying out physical exercise may be restricted by their underlying disease. Similarly, instructions should be given to avoid falls, trauma and excessive effort. It is necessary to follow the general rule that when starting a treatment with GC it should be administered at the lowest efficacious dose and for the shortest time possible.

These guides were subsequently updated and published in 2009. With reference to steroidal osteoporosis, the recommendations of SEIOMM were to maintain the earlier recommendations and specify the existence of 2 new drugs: teriparatide and zoledronate. Taking these into account the recommendation of the panel of experts was to maintain alendronate and risendronate as drugs of first choice, while also including as such zoledronate, if it is considered preferable in the specific circumstances of a case, and to use teriparatide if the risk of fracture is high or if the response is not considered adequate.

5c. Recommendations of other international guides

The American College of Rheumatology and the Royal College of Physicians at an international level have formulated a series of recommendations for the prevention and treatment of osteoporosis induced by glucocorticoids. Among these are included a higher awareness of general health, the administration of calcium and vitamin D supplements, the reduction in the dose of glucocorticoids...
oids to a minimum and, when it is indicated, therapeutic intervention with bisphosphonates and other drugs indicated in this therapy.

The guides of the UK’s Royal College of Surgeons recommend that primary prevention be carried out in all men, and in women more than 65 years old, in individuals with a previous history of fractures, and in younger people with a BMD T-score of ≤ -1.5, who are going to follow a treatment with oral corticoids for at least 3 months69. However, the American College of Rheumatology recommends carrying out prevention in those patients being treated with glucocorticoids with a dose equivalent to 5 mg of prednisone, or higher, a day. These measures include changes in lifestyle, such as quitting smoking or reducing alcohol consumption, carrying out exercise, restricting sodium intake when there is hypercalcemia, and the intake of calcium and vitamin D supplements. The directors of the ARC recommend that treatment with bisphosphonates is initiated in those patients whose T-score is equal to, or less than, -1.068.

6. Conclusions
Prolonged treatment with oral corticoids increases the risk of fragility-related fractures at doses as low as 5 mg/day of prednisone or equivalent, and already at 3 months from the start of treatment. Thus it is necessary to act to prevent the appearance of these fractures.

At the start of a treatment with corticoids one should take into account how much time and at what dose, approximately, the treatment with oral steroids is going to last, as well as the clinical state of the patient.

In all cases it is advisable to indicate general measures, such as the maintenance of physical activity as adequately as possible, a balanced diet with an abundant quantity of milk products, and exposure to the sun for at least 10 minutes a day. If the corticoids are going to be given for more than 3 months and the dose used is at least 7.5 mg/day, a supplement of calcium and vitamin D should be administered.

Alendronate and risedronate are drugs which should be used in the first instance, above all if used as prevention and if the patients do not have fractures or densitometric osteoporosis. There were no available studies which advised on the duration of treatment, but it appears reasonable to maintain it while the patient is taking oral corticoids. Zoledronate is also an excellent initial option, its annual administration being convenient and permitting an adherence to treatment higher than that of other drugs. But its intravenous administration and its use restricted to the ambit of a hospital limits its use.

PTH 1-34 (teriparatide) constitutes an interesting alternative, since it has been shown to be superior to alendronate in the reduction of risk of vertebral fracture. The indication for which it has been approved by the European Medicines Agency is the treatment of secondary osteoporosis due to glucocorticoids in men and women, pre- and postmenopausal, with a high risk of fracture. Its price, and the necessity of parenteral administration makes its use recommendable as a second line drug, when it is not possible to use bisphosphonates, and when the clinical results have not been what was expected. However, in patients with vertebral fractures already present at the time of initiating the steroid treatment, or in those who have a very low BMD and require a long period with oral corticoids at doses higher than 7.5 mg/day, or in premenopausal women who are not able to take other treatments, the initial use of PTH 1-34 could be considered, to be continued later with a bisphosphonate69.

Table 1. “Who to treat”. Recommendations of the GTO-SEMI68

<table>
<thead>
<tr>
<th>Group</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>a) Postmenopausal women:</td>
<td>- In general, patients who are going to receive or are receiving more than 5 mg/day for more than 3 months</td>
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<tr>
<td></td>
<td>- Patients with BMD (measured by DXA) with a T-score lower than -1.5 who are going to receive or are receiving more than 2.5 mg/day for more than 3 months</td>
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<tr>
<td>b) Premenopausal women or males:</td>
<td>- In general, patients who are going to receive or have received more than 7.5 mg/day for more than 3 months</td>
</tr>
<tr>
<td></td>
<td>- Patients with BMD (measured by DXA) with a T-score lower than -1.5 who are going to receive or have received more than 5 mg/day for more than 3 months</td>
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<tr>
<td>c) All patients with previous fractures due to fragility</td>
<td>- Patients with previous fractures due to fragility</td>
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