National Institute for Health and Clinical Excellence (NICE) Final Appraisal Determination Recommends Treatment Options for Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women

Tuesday 8th July 2008: Procter & Gamble Pharmaceuticals (P&GP) welcome the new Final Appraisal Determination (FAD) Guidance for the primary and secondary prevention of osteoporosis from NICE.

The revised NICE FAD recommends risedronate - alongside etidronate - as the *first alternative* treatment option to generic alendronate for postmenopausal women who are unable to comply with the special administration instructions, have a contraindication to, or are intolerant of alendronate (and also meet certain criteria such as BMD T- scores [a measurement of Bone Mineral Density], age and independent risk factors for fracture)[i,ii].

Suggested Treatment Flow[i,ii]

	Primary and Secondary Prevention
First treatment option	Generic alendronate* (T-score ≤-2.5SD)
First alternative	Risedronate* or etidronate*
Second alternative	Strontium ranelate* or raloxifene**
Third alternative	Teriparatide**

* Dependent on age, T score, independent clinical risk factor for fracture, and indicators of low BMD

** Recommended for secondary prevention only

Recommended treatment options are not only based on the clinical efficacy of the therapies but also the acquisition cost of the available osteoporosis medicines and form a clear stepwise process. There are still some complexities within the guidance regarding thresholds for age and level of condition[i,ii]. The Guidance is still in draft form until finalised guidance is issued later this year.

"For some patients, alendronate is not a suitable treatment and it is essential that these individuals have access to other treatments."

Professor Juliet Compston, Professor of Bone Medicine, University of Cambridge

What the revised NICE FAD Guidance says

Previous draft NICE FAD guidance had only recommended alendronate as a treatment option for postmenopausal osteoporosis patients. However this decision was met with opposition from patient groups such as the National Osteoporosis Society (NOS) (please see section notes to the editors). The revised position of the NICE FADs recommend risedronate, alongside etidronate, as the first alternative treatment option following generic alendronate[i,ii]. Strontium ranelate has been recommended as a second alternative therapy only where patients are not able to comply with special instructions for the administration of either alendronate and risedronate or etidronate, or who have a contraindication to or are intolerant of alendronate and risedronate or etidronate[i,ii.]

> *"It remains vitally important that my patients have a choice of therapy as many will get upper gastrointestinal problems with generic alendronate. I am pleased that NICE now supports my prescribing of risedronate where I feel it is the best alternative to alendronate."*
>
> **Dr Pam Brown, The Grove Medical Centre, Swansea**

Why is the revised NICE FAD Guidance important?

The revised position of the NICE FAD Guidance is particularly important for post-menopausal osteoporosis patients as NICE recognise that one third of participants in post-marketing studies of alendronate reported the occurrence of adverse gastrointestinal events[i,ii]. Osteoporosis care should now better meet the needs of individual patients as treatment options have been recognised by NICE for patients who cannot take generic alendronate.

> *"There are significant differences between bisphosphonates, many patients cannot tolerate alendronate and need to be able to receive an alternative treatment like risedronate."*
>
> **Dr Alun Cooper, GPwSI, Bridge Medical Centre, Crawley**

There is a wealth of evidence supporting the efficacy of bisphosphonates as the leading treatment class in the management of osteoporosis. However, not all bisphosphonates have the same tolerability profiles, mode of administration and efficacy at key osteoporotic sites[iii,iv,v]. Managing osteoporosis involves a balance between choosing a treatment that best protects the individual from fracture, has an adequate tolerability profile, and makes best use of NHS resources.

Final Guidance is expected from NICE later this year and without further appeal must be implemented by all healthcare professionals within 3 months of publication.

Notes to editors

- Approximately 80% of patients who could not tolerate alendronate were able to tolerate risedronate[vi]. There are limited data available on switching patients between bisphosphonates. In a randomised, double-blind study of 66 patients that had previously discontinued treatment with 10mg/day alendronate due to upper gastrointestinal adverse events, when switched to risedronate (5mg daily) patients showed a similar incidence of upper GI events to placebo at 3 months[vi].

  Oral bisphosphonates have been associated with upper gastrointestinal disorders. Therefore, risedronate should be used with caution in patients with stricture, achalasia, those with active/recent history of upper gastrointestinal problems and patients who are unable to follow the dosing instructions[iv].

- Nine multicenter, randomized, double blind, placebo controlled studies of risedronate were pooled and evaluated to determine the frequency of upper gastrointestinal (GI) tract adverse events associated with risedronate, especially among high risk patients (those on NSAIDS, PPIs and H2As). The results of this extensive evaluation indicate that among these high risk patients the incidence of upper gastrointestinal adverse events with those on risedronate was similar to that in control patients[vii].

- In June 2007 the previous version of the NICE FADs were published. Despite the length and depth of the consultation NICE failed to incorporate many of the recommendations which their stakeholders had made. The two documents recommended only one of the entire range of treatments that are available for osteoporosis – generic alendronate. In October 2007 independent appeals were made by the National Osteoporosis Society, the Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals and sanofi aventis), and Servier as no alternative treatments were provided for women with osteoporosis who could not tolerate or for whom alendronate was contraindicated. This appeal was successful. Furthermore the NOS presented a petition to Downing Street demanding treatment options for postmenopausal patients with osteoporosis.

- There has been a huge demographic shift in the UK over the past twenty years, so the population is growing older. Consequently, osteoporosis related disability is now highly significant, particularly in terms of patient quality of life, morbidity/mortality costs and the overall socio-economic burden:

  - Three million people are at risk of osteoporosis in the United Kingdom[viii].
  - It is estimated that treating osteoporotic fractures in postmenopausal women costs the NHS and government £1.7 billion a year, the equivalent of £5 million a day[viii].

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About The Alliance for Better Bone Health
The Alliance for Better Bone Health was formed by Procter & Gamble Pharmaceuticals and Aventis part of the sanofi-aventis Group, in May 1997 to promote bone health and disease awareness through numerous activities to support physicians and patients around the globe.

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For P&G: All statements, other than statements of historical fact included in this release, are forward-looking statements, as that term is defined in the Private Securities Litigation Reform Act of 1995. Such statements are based on financial data, market assumptions and business plans available only as of the time the statements are made, which may become out of date or incomplete. We assume no obligation to update any forward-looking statement as a result of new information, future events or other factors. Forward-looking statements are inherently uncertain, and investors must recognize that events could differ significantly from our expectations. In addition to the risks and uncertainties noted in this release, there are certain factors that could cause actual results to differ materially from those anticipated by some of the statements made. These include: (1) the ability to achieve business plans, including with respect to lower income consumers and growing existing sales and volume profitably despite high levels of competitive activity, especially with respect to the product categories and geographical markets (including developing markets) in which the Company has chosen to focus; (2) the ability to successfully

execute, manage and integrate key acquisitions and mergers, including (i) the Domination and Profit Transfer Agreement with Wella, and (ii) the Company's merger with The Gillette Company, and to achieve the cost and growth synergies in accordance with the stated goals of these transactions; (3) the ability to manage and maintain key customer relationships; (4) the ability to maintain key manufacturing and supply sources (including sole supplier and plant manufacturing sources); (5) the ability to successfully manage regulatory, tax and legal matters (including product liability, patent, and intellectual property matters as well as those related to the integration of Gillette and its subsidiaries), and to resolve pending matters within current estimates; (6) the ability to successfully implement, achieve and sustain cost improvement plans in manufacturing and overhead areas, including the Company's outsourcing projects; (7) the ability to successfully manage currency (including currency issues in volatile countries), debt, interest rate and commodity cost exposures; (8) the ability to manage continued global political and/or economic uncertainty and disruptions, especially in the Company's significant geographical markets, as well as any political and/or economic uncertainty and disruptions due to terrorist activities; (9) the ability to successfully manage competitive factors, including prices, promotional incentives and trade terms for products; (10) the ability to obtain patents and respond to technological advances attained by competitors and patents granted to competitors; (11) the ability to successfully manage increases in the prices of raw materials used to make the Company's products; (12) the ability to stay close to consumers in an era of increased media fragmentation; and (13) the ability to stay on the leading edge of innovation and maintain a positive reputation on our brands. For additional information concerning factors that could cause actual results to materially differ from those projected herein, please refer to our most recent 10-K, 10-Q and 8-K reports.

Information about adverse event reporting can be found at www.yellowcard.gov.uk. In the UK adverse events should be reported to Procter & Gamble Pharmaceuticals on 01784 474900. In Ireland adverse events should be reported to sanofi-aventis on 01-4035 600 or DUBDrugSafety@emailph4.aventis.com.

References

[i] National Institute for Health and Clinical Excellence, Alendronate, etidronate, risedronate, raloxifene, and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Final Appraisal Determination, July 2008

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[vii] Taggart H, *et al. Mayo Clin Proc.* 2002; **77**: 262-270

[viii] National Osteoporosis Society, Annual Report 2007 http://www.nos.org.uk/NetCommunity/Document.Doc?id=100