Senate Community Affairs References Committee

Inquiry into Consumer Access to Pharmaceutical Benefits

Introduction

Sanofi-aventis welcomes this opportunity to submit to the Community Affairs Reference Committee Inquiry into Consumer Access to Pharmaceutical Benefits.

Sanofi-aventis Australia/New Zealand is an integrated healthcare provider with an extensive range of products ranging from patented medicines in disease areas including oncology, diabetes, cardiovascular disease and osteoporosis, to generic medicines, vaccines, over the counter medicines and complementary medicines.

Our company manufactures and distributes a medicine called "Actonel®" (risedronate), which is used to treat bone disease such as osteoporosis. Actonel® belongs to a group of medicines called bisphosphonates which prevent the loss of bone mass.

Summary

Sanofi-aventis opposes the continued creation of therapeutic groups on the Pharmaceutical Benefits Scheme (PBS), including formation of an oral bisphosphonates therapeutic group.

Therapeutic groups potentially shift costs to patients and introduce cost as a consideration in doctor's prescribing decisions. They also undermine the extensive reforms already undertaken to deliver sustainability for the PBS and lead to greater uncertainty when companies look to bring innovative new medicines to the Australian market.

Our company disputes that oral bisphosphonate medicines are interchangeable at the individual patient level and maintains that there are well documented and important chemical, biochemical and pharmacological differences between these medicines which mean that they are not interchangeable. There are also significant concerns about the lack of process and stakeholder consultation in determining medicines to be interchangeable.

Therapeutic Groups

In November 2009, the government announced its intention for oral bisphosphonate medicines reimbursed on the Pharmaceutical Benefits Scheme (PBS) to be formed into two therapeutic groups – an osteoporosis therapeutic group and Paget disease therapeutic group.

Medicines contained in each therapeutic group include:

Osteoporosis therapeutic group

- Alendronate sodium 70mg, Fosamax Once Weekly® (and many other generic brands)
- Alendronate sodium 70mg with colecalciferol 70 micrograms, Fosamax Plus®
- Alendronate sodium 70 mg with colecalciferol 140 micrograms, Fosamax Plus 70 mg 140 mcg®
- Alendronate sodium 70 mg with colecalciferol 140 micrograms and calcium carbonate 2.5g, Fosamax Plus COMBI®
- Risedronate sodium 5 mg, Actonel®
- Risedronate sodium 35 mg Actonel Once-a-Week®
- Risedronate sodium 75 mg, Actonel® 75 mg
- Risedronate sodium 150 mg, Actonel Once-a-Month®
- Risedronate sodium 35 mg and calcium carbonate 1.25 g, Actonel Combi®
- Risedronate sodium 35 mg and calcium carbonate 2.5g with colecalciferol 22 micrograms, Actonel Combi D®

Paget disease therapeutic group

- Alendronate sodium 40 mg, Fosamax 40mg®
- Risedronate sodium 30 mg, Actonel®
- Tiludronate disodium, equivalent to 200 mg tiludronic acid, Skelid®

Therapeutic groups contain medicines that the Pharmaceutical Benefits Advisory Committee (PBAC) – the independent statutory body that makes recommendations to the Health Minister about medicines listed on the PBS - has advised the Minister are interchangeable at the individual patient level. Because therapeutic group medicines provide the same health outcome for patients, the price paid by government for those medicines is based on the cost of the lowest priced medicine in the group, regardless of whether or not a medicine is still on patent.

However, in the case of the recently announced oral bisphosphonate therapeutic groups, sanofi-aventis disputes the decision that bisphosphonate medicines are interchangeable at the individual patient level. We maintain that the process (or lack of process) in determining medicines to be interchangeable, and therefore eligible for inclusion in therapeutic groups, is inadequate.

It is critical for the health and safety of Australian patients that any proposal for one medicine to be used in place of another be subjected to a rigorous and transparent evaluation process. This process must include independent assessment of all available clinical data and consultation with concerned stakeholders including expert clinicians, patients, patient groups and medicines manufacturers.

Osteoporosis in Australia

Osteoporosis occurs when bones lose calcium, minerals and microarchitecture more quickly than the body can replace them. Bones become brittle and at high-risk of fracture from minor falls or bumps. Osteoporosis is most common in women, particularly those post-menopause aged 65 years and older, but it also affects men.

Osteoporosis is an often under-recognised and undertreated disease that has a devastating impact on the quality of life and independence of its mainly elderly patients. Many people are unaware that they have the condition until they suffer their first fracture, and after a first fracture, the chance of another fracture is doubled[1].

Up to twenty per cent of elderly patients in Australia will die within one year of sustaining a hip fracture and of those patients who do not die, 50 per cent will require long-term assistance and 25 per cent will require full-time nursing-home care[2].

It is estimated that one in two Australian women and one in three men over the age of 60 will suffer a fracture due to osteoporosis. At present, there may be up to 2.3 million Australians with osteoporosis, with this number expected to increase to 3 million people by 2020. It is estimated that there will be almost 600,000 hospitalisations due to osteoporotic fractures over the next decade at a cost of $300 million[3], with total annual direct costs associated with fractures estimated at $1.9 billion[4].

Osteoporosis can be treated with bisphosphonate medicines which may help reverse its progression. Bisphosphonate medicines work by slowing down the process of old bone being removed and help to rebuild bone mass, creating stronger bone which is less likely to fracture[5]. Persistence in taking bisphosphonate medicines is critical to success in treating osteoporosis, but patient compliance with treatment regimens remains a significant problem[6].

Inquiry terms of reference

1. the impact of new therapeutic groups on consumer access to existing PBS drugs, vaccines and future drugs, particularly high cost drugs;

Medicines stakeholders are agreed that is it essential to ensure the sustainability of the PBS and in 2007, the medicines industry supported government reforms to achieve PBS savings of up to $6 billion over 10 years[7]. These reforms were based on recouping savings from older off-patent or generic medicines, while providing pricing certainty for innovative new, on-patent medicines.

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[1] Marshall D, Johnell O, Wedel H (1996) *Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures*, British Medical Journal 312:1254-1259.
[2] Osteoporosis Australia (2007) *The Burden of Brittle Bones: Epidemiology, Costs and Burden of Osteoporosis in Australia*, Prepared by the Department of Medicine, University of Melbourne, Western Hospital, Footscray, Victoria, September.
[3] Access Economics (2010) *A future less fragile*, Report for Novartis Australia Pty Ltd, http://www.accesseconomics.com.au/publicationsreports/showreport.php?id=227&searchfor=2010&searchby=year
[4] Osteoporosis Australia (2007) et al.
[5] ACTONEL®, ACTONEL COMBI & ACTONEL COMBI D - Product Information – sanofi-aventis Australia pty ltd; last updated: Friday, May 22, 2009.
[6] Access Economics (2010) et al.
[7] Centre for Strategic Economic Studies (2009) *The impact of PBS reforms on PBS expenditure and savings*, Victoria University.

However, the continued application of therapeutic groups policy to the PBS leads to considerable uncertainty for medicines manufacturers. For example, the policy means that even though a medicine manufacturer may have proven a medicine to be cost-effective to have it listed on the PBS, the company may be surprised at some later point by that medicine being linked in price to a generic medicine, even though the patent of the medicine is still valid. This uncertainty impacts decisions including whether or not to pursue the listing of innovative new medicines or improved formulations of medicines in Australia and the viability of continuing supply of those medicines affected by therapeutic groups.

Therapeutic groups link medicines together for pricing purposes on the basis that the medicines within the group are interchangeable and deliver the same health outcome for individual patients. The government pays only the price of the lowest priced medicine within the group - regardless of whether or not a medicine is still on patent.

Given the arbitrary manner in which therapeutic groups may be created and the automatic reductions in prices paid for medicines with the group, balanced against the significant cost involved in bringing a new medicine to market, this lack of predictability may undermine market certainty in seeking to list new medicines in Australia.

In the case of oral bisphosphonates, the creation of a therapeutic group means that in the future, a company with a new bisphosphonate medicine may decide not to list in Australia because they would have to accept a price based on that of the lowest cost medicine in the group.

Alternatively, even if their medicine has health benefits above those bisphosphonates already available on the PBS, they may still be discouraged from listing as their price will be referenced to that of the lowest cost medicine in the group. This could lead to a reduction in Australian patients' choice of medicines, and potential for patients to miss out on medicines with additional health benefits.

2. the criteria and clinical evidence used to qualify drugs as interchangeable at a patient level;

Sanofi-aventis has not been provided with any information about the clinical evidence used to determine the interchangeability of different oral bisphosphonate medicines at the individual patient level. We note that the medicines included in the therapeutic groups have been listed on the PBS since 2001 and until now, there has never been a suggestion that they should be considered interchangeable at the individual patient level.

Our company asserts there is no scientific or clinical rationale for considering bisphosphonate medicines to be interchangeable at the individual patient level. In fact, there are significant differences between oral bisphosphonate medicines in terms of speed of onset of protection, fracture risk reduction at specific skeletal sites and speed of reversal of effects to name a few, all of which are highly clinically relevant in determining suitable bisphosphonate treatment for individual patients.

In clinical practice, physicians take into consideration various individual characteristics of each patient: the age, the severity of the disease and the co-morbidities, presence of concomitant medications, patient's lifestyle and dietary habits, as well as the likelihood of compliance with the therapy.

Different molecules and/or different presentations of medicines are more appropriate for some individuals than others, and hence are not "interchangeable on an individual patient basis". The use of different molecules and/or different presentations irrespectively of the patients' characteristics may have significant safety implications for patients.

In terms of the oral bisphosphonate medicines therapeutic groups, there are well documented and important chemical, biochemical and pharmacological differences between medicines which mean they are not interchangeable[8]. These differences include:

Onset of fracture protection

Different bisphosphonate medicines act in different ways and at different speeds when taken by patients. Faster acting bisphosphonates are obviously the most appropriate medicine for those patients who have just sustained a fracture and are at a very high risk of sustaining another fracture[9]. Only one bisphosphonate has shown that it can reduce the risk of fractures within 6 months[10] [11]. Similarly, only one bisphosphonate medicine has shown evidence of anti-fracture efficacy in patients aged 80 and over, which means the use of another bisphosphonate medicine could result in suboptimal fracture protection and an increased risk of fracture[12].

Bisphosphonates and hip fracture protection

Only one of the bisphosphonate medicines in the therapeutic group has demonstrated efficacy in reducing the incidence of hip fracture in elderly men or women after a stroke[13] [14], in elderly women with Alzheimer's disease[15], and in elderly men with

[8] Russell RG et al. M*echanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy*. Osteoporosis International 2008; 19(6):733-759.
[9] Johnell O, et al. *Acute and Long-Term Increase in Fracture Risk after Hospitalization for Vertebral Fracture.* Osteoporosis International 2001; 12:207-214.
[10] Roux C et al. *Efficacy of risedronate on clinical vertebral fractures within six months*. Current Medical Research & Opinion 2004; 20(4):433-439.
[11] Harrington JT et al. *Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis*. Calcified tissue international 2004; 74(2):129-135.
[12] Boonen S. M. *Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: Implications for the use of antiresorptive agents in the old and oldest old*. Journal of the American Geriatrics Society 2004; 52(11):1832-1839.
[13] Sato Y. *Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke*. Archives of Internal Medicine 2005; 165(15):1743-1748.
[14] Sato Y. et al. *Risedronate therapy for prevention of hip fracture after stroke in elderly women.* Neurology 2005, 64(5): 811-816.
[15] Sato Y. *The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: A randomized controlled trial*. Archives of Internal Medicine 2005; 165(15):1737-1742.

Parkinson's disease[16]. This is of particular importance in these groups of patients; because of their frailty and their increased risk of falls, they are at a greater risk of hip fracture.

Reversal of Effect

The ability to quickly reverse the effect of medicines is important in treating some types of patients, but the rate of reversal varies between different bisphosphonate medicines. This is a very important issue for patients undergoing high-dose glucocorticoid therapy such as in the first months after organ transplantation. The ability to quickly reverse the impact of bisphosphonates is also important in women of childbearing age, where one does not want the possibility of bisphosphonates crossing the placenta to the foetus.

Gastrointestinal tolerability

Some bisphosphonate medicines may cause gastrointestinal problems for patients, which creates a risk that patients may not comply with their medicine regime and increase their risk of an osteoporotic fracture. Many patients who cannot tolerate one oral bisphosphonate are able to tolerate the other[17]. Given this difference in tolerability, in those patients with a history of gastrointestinal problems such as reflux disease, clinicians prefer to prescribe those oral bisphosphonates that are better tolerated.

Additional vitamins and supplements with bisphosphonates

Calcium and vitamin D are an essential component of the management of osteoporosis in patients who are calcium and/or vitamin D deficient. Sanofi-aventis' osteoporosis medicine Actonel® comes in a range of different formulations, including combinations with Vitamin D and/or calcium, which are provided free of charge to patients.

The combination pack with calcium is prescribed to osteoporotic patients who have inadequate calcium intake, whereas patients who are both vitamin D deficient and have an inadequate calcium intake would require the alternate combination with calcium and vitamin D. A study from 2008, looking at differences in fractures in an osteoporotic population treated with bisphosphonates, found patients treated with bisphosphonates and supplements (Vitamin D and calcium) were associated with a reduced incidence of fractures compared with those patients treated with bisphosphonates and no supplements[18]. Hypocalcaemia (abnormally low calcium levels) can be a serious medical problem and some patients with inadequate dietary calcium intake may be relying on the calcium supplements that come with their oral bisphosphonate medicine.

However, not all the medicines within the proposed oral bisphosphonate therapeutic group come with these equivalent combinations of Vitamin D and/or calcium. This means that they are not interchangeable for patients and that substituting these medicines could put patients' safety at risk.

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[16] Sato Y et al. *Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease*. Neurology 2007; 68(12):911-915.

[17] Adachi JD et al. *Tolerability of risedronate in postmenopausal women intolerant of alendronate*. Aging. 2001 ;13(5):344-6.)

[18] Adami S, *Vitamin D and response to treatment in postmenopausal osteoporosis*, Future Rheumatology. (2008) 3(5), 407-408.

Daily, weekly and monthly bisphosphonate treatment packs

The bisphosphonate medicines in the therapeutic groups come in a number of different formulations including daily, weekly and monthly packs. A monthly dosing regimen is a particularly useful option in elderly patients who require supervision to ensure that their oral bisphosphonate is taken in accordance with the dosing instructions. Patients treated with a monthly oral bisphosphonate are 37 per cent less likely to be non-persistent and 5 per cent more compliant than patients treated with a weekly regimen[19], which equates to better fracture protection. Only one of the medicines in the therapeutic group has a once monthly treatment regimen reimbursed on the PBS.

Differences in PBS indications

There are important differences in approved PBS indications between oral bisphosphonates. In particular only one oral bisphosphonate is PBS listed for treatment of patients on long term, high dose corticosteroid. As no other oral bisphosphonate medicine is reimbursed on the PBS for this condition, it cannot be interchangeable at the individual patient level for this indication.

3. the effect of new therapeutic groups on the number and size of patient contributions;

While the inclusion of medicines in therapeutic groups means the government reimburses suppliers of those medicines at only the cost of the lowest priced medicine in the group, it also allows for suppliers to apply a premium above the reimbursed price for their medicines.

A premium applied above the reimbursed price is paid for by patients and is in addition to the co-payment of $5.40 per script for concessional patients and $33.30 per script for general patients, already paid by Australian consumers.

The presence of patient premiums for medicines could introduce financial considerations into doctors' prescribing decisions. Further, the introduction of premiums payable by patients can also impact their adherence to drugs regimens. If patients are financially forced to forgo or substitute treatment for a medicine which does not provide the best therapy for their circumstances, it may cause an increased burden on the health system through increased incidence of fractures.

4. consultation undertaken in the development of new therapeutic groups;

Sanofi-aventis is deeply concerned by the lack of consultation or formal process in the creation of new therapeutic groups on the PBS. Our company is opposed to the continuation of therapeutic groups, but believes that while this policy is in place, proposals to form therapeutic groups based on the interchangeability of medicines must

[19] Cotte FE et al., *Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis*, Osteoporosis Int. 2010 Jan;21(1):145-55. Epub 2009 May 21.

be subject to the same rigorous scrutiny that applies to all medicines registration and reimbursements in Australia.

Sanofi-aventis has strongly supported changes over the last two years to provide greater transparency around PBAC processes, including the publication of the PBAC agenda, and opportunity for clinical experts, patients and patient organisations to comment on medicines listing proposals. It is disappointing that similar transparency and regard for the opinions of clinical experts and Australian patients is disregarded in the case of therapeutic groups policy.

In the case of the oral bisphosphonate osteoporosis and Paget disease therapeutic groups; while the PBAC provided advice to the Minister in June 2009 that these groups should be formed, there was no consultation with our company about the clinical implications for patients or the commercial impact of the decision. Sanofi-aventis received no communication about the proposal until it was announced in the Mid-Year Economic and Fiscal Outlook on 2 November 2009 – five months after the recommendation was made. At that time sanofi-aventis were informed that the new therapeutic groups would be created in December 2009, and that any comments about the proposed group should be made within 18 days. Our company responded by asking that the therapeutic groups not be formed until the PBAC had considered all relevant information.

On 3 December, the Secretary to the PBAC invited sanofi-aventis to provide further comments about clinical issues by 16 December, to be considered and advised on by the PBAC by 7 January 2010. Sanofi-aventis provided further comment, but contended that 13 days notice was insufficient time for the preparation of a fully-developed, evidence-based submission; nor did the proposed process of PBAC consideration of clinical issues over the Christmas and New Year period provide for standard independent evaluation of clinical evidence. This proposed timeline and process in no way reflected either the months of work that go into preparation of a PBAC submission, the typical 17-week cycle of independent evaluation of submissions to the PBAC or the 255 working-days process for TGA registration of medicines.

Our company advised the PBAC Secretary of our intention to submit detailed clinical data disputing the interchangeability of bisphosphonate drugs in the form of a major submission to the PBAC, to be completed in time for the March 2010 deadline, for consideration at the July 2010 PBAC meeting. Given the serious clinical issues and evidence that would be discussed in that major submission, sanofi-aventis requested that no action be taken to progress the formation of the therapeutic groups until all clinical data had been independently evaluated and the PBAC considered that submission in full.

Sanofi-aventis was not surprised to learn that on 8 January, the PBAC reaffirmed its advice that the bisphosphonate therapeutic groups should be formed and our company has continued to maintain that the measure should not proceed until consideration of our major clinical submission to the PBAC in July 2010.

The years of research in conducting clinical trials in medicines and analysing patient trial data, along with the ongoing collection of real-world medicines useage data undertaken

by manufacturers is critical to the registration and reimbursement of medicines in Australia. It is the strong belief of sanofi-aventis that decisions about interchangeability of medicines and formation of therapeutic groups should not occur without the same rigorous consultation with medicines manufacturers that is required for any medicines registration or reimbursement.

5. the impact of new therapeutic groups on the classification of medicines in F1 and F2 formularies;

As discussed above, the medicines industry supported major reforms of the PBS in 2007 to ensure its ongoing sustainability. According to analysis commissioned by both the Department of Health and Ageing and Medicines Australia those reforms will achieve savings of up to $6 billion over 10 years[20] [21]. Under those reforms, medicines were separated into two formularies – F1 containing innovative, on-patent medicines and F2 containing older, generic medicines. Savings are to be achieved through the capture of price reductions on older F2 medicines, while providing pricing certainty for innovative medicines on F1.

However, the continued creation of therapeutic groups on the PBS means that medicines listed in the F1 formulary under the 2007 reforms, can be arbitrarily shifted to F2, with a corresponding reduction in their reimbursed price, regardless of whether or not they are still patent protected.

The therapeutic groups policy undermines the spirit of the 2007 PBS reforms which were negotiated in good faith by the medicines industry and creates continuing uncertainty about the medicines reimbursement environment in Australia. Most major pharmaceutical companies in Australia are affiliates of global organisations for whom the stability of the reimbursement environment is a major factor in determining the likelihood and timeframe for pursuing listing of new and innovative medicines, the supply of existing medicines, as well as ongoing investment in research and development.

Conclusion

Sanofi-aventis opposes the continuation of therapeutic groups on the PBS, and in the case of the recently created bisphosphonate therapeutic groups, maintains that the medicines in the group are not interchangeable and that there has been a lack of process and failure to consult or follow standard processes in the creation of the new therapeutic groups.

[20] Price Waterhouse Coopers (2010) *The impacts of Pharmaceutical Benefits Scheme Reform*, Department of Health and Ageing.
[21] Centre for Strategic Economic Studies (2009) et al.

Our company recommends:

1. That the policy of therapeutic groups on the PBS be abolished, including the removal of existing therapeutic groups and the discontinuation of formation of new therapeutic groups, including the oral bisphosphonates therapeutic groups;

2. If therapeutic group policy continues that:
    a. The PBAC reconsider its advice that oral bisphosphonates therapeutic groups should be formed;
    b. Therapeutic groups must not be formed between on-patent (F1) and non-patented (F2) medicines;
    c. A medicine on patent can not be shifted from the F1 to F2 formulary for the purpose of forming a therapeutic group;
    d. Any proposal to form a therapeutic group must be subject to the same rigorous process and timeframe as that provided for registration of medicines;
    e. Any proposal to form a therapeutic group must provide for independent evaluation of clinical data and a transparent consultation process with all affected stakeholders before a recommendation is made by the PBAC.