The Government's Administration of the Pharmaceutical Benefits Scheme (PBS)

Mundipharma Pty Limited Submission to the Senate Inquiry: July 2011

Senate Finance and Public Administration References Committee Inquiry

Senate Finance and Public Administration References Committee inquiry into:

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Attachments

Attachment 1: Current membership of the Pharmaceutical Benefits Advisory Committee

Abbreviations

AMA	Australian Medical Association
CHF	Consumer Health Forum
DoHA	Department of Health & Ageing
DUSC	Drug Utilisation Sub-Committee
EAPC	European Association for Palliative Care
GP	General Practitioners
MoU	Memorandum of Understanding
NMP	National Medicines Policy
OIBD	Opioid-induced bowel disease
OIC	Opioid-Induced constipation
PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
PBS	Pharmaceutical Benefits Scheme
PR	Prolonged release
QoL	Quality of Life

Senate Finance and Public Administration References Committee inquiry into: The Government's Administration of the Pharmaceutical Benefits Scheme (PBS)

Executive Summary

The provision of safe and affordable medicines to Australians has been well-served since the Pharmaceutical Benefits Scheme (PBS) was first introduced in 1948.

More recently the cost of operating the Scheme has been widely debated and, in the light of "current fiscal circumstances" policy decisions have been taken which change the process by which new medicines are PBS listed. Particularly, all medicines recommended by the Pharmaceutical Benefits Advisory Committee (PBAC) for listing on the PBS with a potential cost impact to the PBS are now referred to Cabinet for a determination on whether the positive PBAC recommendation should be implemented, or not, and when. That is, the longstanding threshold of $10 million incremental cost to the PBS triggering referral to Cabinet has been removed.

This policy decision was implemented without any prior discussion or consultation with those companies directly affected and with no apparent regard for the health and welfare of chronically ill patients and any flow on logistical and financial consequences for the businesses impacted.

More disturbingly, parallel decisions have been taken by Cabinet to *defer indefinitely* the implementation of a number of PBAC listing recommendations, impacting the health and welfare of a broad community of patients suffering a wide range of illness. The process whereby some new medicines are given the 'green light' for PBS listing by Cabinet and others not remains a mystery, and does nothing to enhance the transparency of the process.

Mundipharma can only echo the sentiments expressed by the Australian Medical Association (AMA) and Consumer Health Forum (CHF) in their recent joint statement in this matter:

"…for Cabinet to be choosing to list some medicines on the PBS and not others raises the question of what expertise and experience they have that enables them to make decisions

that contradict the advice of their own expert committee of clinicians and health economists."

Neither does this new policy decision provide enhanced certainty or stability in the pharmaceutical industry business environment that was anticipated and welcomed following the signing of the Memorandum of Understanding (MoU) last year between the Commonwealth and Medicines Australia. An agreement set to deliver $1.9 billion cost savings to the PBS – savings designed, at least in part, to ensure 'headroom' is assured for the PBS listing of new, innovative medicines.

Mundipharma continues to be dismayed that, over four (4) months since the Minister's public announcement of the listing deferrals of a number of new medicines on the PBS, we are no closer to receiving any commitment from Government on when the PBS listing of Targin® tablets will proceed. This unprecedented decision continues to impact on patients suffering severe disabling pain.

Whilst Mundipharma has been led to understand the basis of the decision by Cabinet was a financial one, we believe this is an unfortunate policy development that sacrifices the health of a vulnerable group of Australians for what most would consider an immaterial saving within the context of the Federal budget.

- Targin® tablets have been subject to a thorough review for safety, efficacy and quality by the Australian Therapeutic Goods Administration (TGA) and are registered by the TGA for use in Australia.
- The **TGA approved indication** for Targin® tablets is **"The management of moderate to severe pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation."**
- The Pharmaceutical Benefits Advisory Committee (PBAC) has thoroughly reviewed extensive and robust health economics data, and has accepted that **Targin® tablets are cost-effective at the price requested**. PBAC has recommended that Targin® tablets be listed on the Pharmaceutical Benefits Scheme (PBS) as Pharmaceutical Benefit item.

- The price for Targin® tablets on the PBS has been approved by the Pharmaceutical Benefits Pricing Authority (PBPA).
- All documentary requirements of the PBS Listing Section have been completed.
- Following PBAC's positive recommendation for PBS listing, the Targin® tablets proposed listing was referred to Cabinet for consideration, even though the estimated the net (incremental) cost to the PBS of listing Targin® tablets is less than $10 million in year five (5) of listing.
- The cumulative net incremental cost to Government of listing Targin® tablets on the PBS is estimated at $22.1 million, compared with the Federal budget over the same period of ~$1.5 trillion.
- Cabinet has taken the decision to *defer indefinitely* seven PBS listings for medicines similarly registered in Australia and recommended for PBS listing by PBAC, **including Targin® tablets**. This decision is unprecedented in that this is the first time that Cabinet has disregarded the recommendations of the peak body responsible for making decisions on medicines. The PBAC determined that Targin® tablets offer significant clinical benefit and are cost-effective ('value for money') compared with other treatments or products for the same condition.
- There is no indication from the Minister's office on when Targin® tablets will be PBS listed, only that Targin® tablets "…will be considered for listing when circumstances permit".

Targin® tablets are a unique and novel approach for selectively and locally antagonising the gastrointestinal effects of opioids involving the co-administration of a μ -opioid receptor antagonist with negligible systemic availability, oral naloxone, with an opioid. Combination therapy with prolonged release (PR) oxycodone plus PR naloxone has been shown to provide effective analgesia while preventing, frequently difficult to manage, OIC – a cause of considerable distress, worry and loss of quality of life (QoL) for chronic severe pain patients being administered long-term opioid analgesia.

It is precisely because of the lack of suitable alternatives to treat OIC that Mundipharma initiated a lengthy and costly research program to develop a superior treatment, superseding out-dated existing and inadequate pharmacological treatments i.e. laxatives, to address this important therapeutic need.

It is regrettable the key decision makers in the Department of Health & Ageing (DoHA) who are advising Government, appear to be misinformed about the substantial shortcomings and

limitations of laxative treatment for the treatment of OIC; that Targin® tablets represent a considerable and innovative advance over existing treatment modalities; and, also appear to misunderstand the basic pharmacological principles through which Targin® tablets are able to exert their action to prevent this distressing side effect of opioids and, consequently, this adverse health consequence of opioid analgesic treatment.

For example, it was reported in Hansard that on the 31st May 2011, the Deputy Secretary of DoHA advised the Senate Community Affairs Legislation Committee that "Targin is oxycodone, which is regularly prescribed for that indication, with naloxone which has a laxative effect. It is equivalent to taking oxycodone in its usual form and a laxative."

It is unfortunate that the formulation and mechanism of action of Targin® tablets should be misrepresented in this way. Targin® tablets are not a strong opioid analgesic combined with a laxative. Targin® tablets are unique in being the only strong opioid analgesic proven to prevent OIC. That is, it prevents an opioid (in this case, oxycodone) from causing constipation in the first place rather than attempting to induce a bowel movement symptomatically once constipation has become a problem.

There is a fundamental, and important, difference between these two treatment algorithms – particularly for chronic pain patients, in that Targin® tablets remove this side effect at cause.

Other misrepresentations made by the Deputy Secretary of DoHA to the Senate Community Affairs Legislation Committee on 31st May 2011, also require to be corrected.

Contrary to the advice provided to the Senate Community Affairs Legislation Committee that there would be no savings from reduced incidence of opioid induced constipation following the PBS listing of Targin® tablets, Mundipharma would take this opportunity to note that the forward estimate agreed with DUSC indicates that there will be a saving of $6.5m over five years as a result of a reduction in opioid induced constipation, resulting from fewer GP and specialist consultations as well as fewer hospital procedures for the most severely constipated patients.

Similarly, in response to a question "What about the total savings that you would have in relation to the abuse and diversion of OxyContin?" following the PBS listing of Targin® tablets, it was claimed

that the Government "would not have figures" showing savings from reductions in abuse and diversion. However, Mundipharma and the DoHA had already agreed there will be a saving of $8.4m over five years from a reduction in abuse of Oxycontin tablets.

It is of concern to Mundipharma that such an important decision to withhold the listing of Targin® tablets on the PBS, to the serious detriment of chronic severe pain patients around Australia, may have been made upon the basis of unsound advice provided to Government.

Mundipharma appreciates the opportunity to contribute to this Senate Inquiry and believes its submission can serve as a Case Study on the impact that changes to the PBS listing process and subsequent PBS listing *indefinite deferrals* are having on both patients and sponsor companies.

We commend this submission to the Committee and urge that the Committee recommend to the Government that the policy of *infinite deferral* of medicines recommended for listing on the PBS be abolished.

Additionally, we trust it will be clear from this document that the PBS listing of Targin® tablets should be made a priority and proceed immediately, and we request the Committee recommend accordingly.

(A) The deferral of listing medicines on the PBS that have been recommended by the Pharmaceutical Benefits Advisory Committee;

The Pharmaceutical Benefits Advisory Committee (PBAC) is an independent statutory body of experts established under section 101 of the National Health Act 1953. For the benefit of the Senate Committee, the current PBAC membership is provided at Attachment 1.

Section 101 of the National Health Act 1953 provides that the PBAC must make recommendations to the Minister within a clearly defined set of criteria. It is worth highlighting for the Committee the following extract from the National Health Act:

(3A) For the purpose of deciding whether to recommend to the Minister that a drug or medicinal preparation, or a class of drugs and medicinal preparations, be made available as pharmaceutical benefits under this Part, the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations.

(3B) Without limiting the generality of subsection (3A), where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee:

> *(a) shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, **provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies**;*

As stated at part 3B(a) of the Act – the PBAC shall not recommend a medicine for listing unless it is satisfied the therapy provides a significant improvement in efficacy. It therefore stands to reason that to arbitrarily withhold from the PBS the listing of any medicine that ***provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies***, and recommended by the PBAC as cost-effective, cannot be in the best interests of patients suffering health issues. Neither can it be in the best interests of society, nor can it be good health policy. To take an opposing view, would require an argument to be mounted that medicines have no meaningful role to play in the health and wellbeing of individual patients or society as a whole. Clearly, such an argument would be unsustainable.

Consequently, notwithstanding current fiscal circumstances, it remains incomprehensible to Mundipharma that, having *deferred indefinitely* seven (7) PBS listings recommended by PBAC at its November 2010 meeting, six (6) of these remain deferred including Mundipharma's Targin® tablets for the concomitant treatment of chronic severe pain and associated opioid-induced constipation.

(B) Any consequences for patients of such deferrals;

Mundipharma thanks the Committee for the opportunity to explain in some detail why the ongoing deferral of PBS listing of important, innovative medicines has adverse health consequences for patients. Our comments to this question are necessarily restricted to the adverse health consequences of withholding Targin® tablets from the Pharmaceutical Benefits Scheme.

Chronic pain in Australia

Mundipharma would note for the Committee that chronic pain affects 1 in 4.5-5.5 Australians (17.9% to 22%)[1,2], 1 in 5 (20%) women and 1 in 6 (17.1%) men in Australia[3]. Of patients with chronic pain, 70% are treated with oral medications and 10% with injected medications.

Approximately 15% of chronic pain sufferers are treated with an opioid or a combined opioid analgesic (8% with a combined opioid analgesic – prescription only combinations of paracetamol plus dextropropoxyphene or higher doses of codeine, and 2% with an opioid analgesic).[1] Chronic pain occurs in up to 70% of patients with advanced cancer, and in approximately 65% of patients suffering from terminal non-malignant disease.[4]

Individuals with chronic severe disabling pain are already suffering immeasurably through inadequate numbers of pain specialists and pain clinics through which they might receive specialist treatment, adding to the significant burden on primary care General Practitioners. Furthermore, the crippling pain often prevents these unfortunate individuals from performing basic activities in and around their home, and can deprive them of the ability to perform paid work resulting in social isolation. All of these factors combine and often manifest themselves in clinical depression, thus triggering more medical treatments and medication.[5]

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[1] Blyth FM, March LM, *et al* (2003). "Chronic pain related disability and use of analgesia and health services in a Sydney community." MJA **179**: 84-87.

[2] Currow DC, Agar M, *et al* (2010). "Chronic pain in South Australia – population levels that interfere extremely with activities of daily living." Australian and New Zealand Journal of Public Health **34(3)**: 232-239.

[3] Blyth FM, March LM, *et al* (2001). "Chronic pain in Australia: a prevalence study." Pain **89**: 127-134.

[4] Colvin L, Forbes K, *et al* (2006). "Difficult pain." BMJ **332**: 1081–1083.

[5] Access Economics Report (2007). The high price of pain: the economic impact of persistent pain in Australia.

Chronic pain is associated with anxiety, depression, loss of independence, and interference with work and relationships.[6]

In many instances, only strong opioid analgesics can provide a measure of relief and restoration of daily function.[7] However, strong opioid analgesics, whilst being an effective treatment for pain relief, are also associated with important adverse effects including opioid-induced bowel dysfunction (OIBD), often including severe opioid-induced constipation (OIC), and the potential for addiction. There is a pressing need to make available to Australians suffering chronic severe pain, a strong opioid analgesic that provides the necessary analgesia and that, at the same time, ameliorates the almost inevitable constipation resulting from treatment with opioids.

Opioid-induced bowel dysfunction (OIBD) and opioid-induced constipation (OIC)

Opioid-induced bowel dysfunction (OIBD) describes the cluster of symptoms characterised by hard dry stools, straining, incomplete evacuation (collectively opioid-induced constipation or OIC), bloating, abdominal distension and increased gastro-oesophageal reflux.[8] Not only is it distressing to patients, but it also leads to physical and functional deterioration amongst long term opioid-medicated patients. Severe constipation can lead to impaction and subsequent hospitalisation.[9] While many side effects occur at the beginning of pain treatment and are attenuated or even disappear over time, constipation persists or can even get worse[8]. A meta-analysis of 41 randomised trials involving 6,019 patients found that there were only two side effects of opioids that were both clinically and statistically significant, nausea and constipation.[10]

[6] Glajchen M (2001). "Chronic pain: treatment barriers and strategies for clinical practice." J Am Board Fam Pract **14**: 211–218.

[7] Riley J, Eisenberg E *et al* (2008). "Oxycodone: a review of its use in the management of pain." Curr Med Res Opin **24(1)**: 175-192.

[8] Kurz A and Sessler DI (2003). "Opioid-induced bowel dysfunction pathophysiology and potential new therapies." Drugs Ageing **63**(7): 649–671.

[9] Candrilli SD, Davis KL & Iyer S (2009). "Impact of constipation on opioid use patterns, health care resource utilization and costs in cancer patients on opioid therapy". J Pain Pall Care Pharmaco **23(3)**: 231-241.

[10] Furlan JC, Urbach DR, *et al* (2007). "Optimal treatment for severe neurogenic bowel dysfunction after chronic spinal cord injury: a decision analysis." British Journal of Surgery **94(9)**: 1139-1150.

Constipation aggravates cancer pain and results in a pattern of increasing opioid dosages in an attempt to relieve pain. The increased opioid dosages only serve to exacerbate the constipation and decreases opioid effectiveness.[11]

As explained above, treatment of chronic severe pain with strong analgesic opioids is frequently associated with constipation – often severe. Approximately one third of patients' consider constipation to be the most debilitating adverse effect associated with opioid therapy for the management of chronic pain.[12]

During discussion at a Pain Management Conference in Melbourne (Oct 2009) a group of leading pain specialists reported that all patients ingesting an opioid experience some form of constipation. It was also noted that patients are reluctant to discuss their constipation either due to embarrassment or because they felt it was a side-effect that they needed to endure. The majority of patients therefore self-medicated. The importance of treating OIC is evident in palliative care protocols and various Guidelines. All specialists agreed with the literature in terms of OIC needing to be treated prophylactically.

Current treatment of opioid-induced constipation (OIC)

A well-recognised source of guidance is the European Association of Palliative Care Research Network (EAPC) which have published recommendations for treating adverse effects associated with opioids.[13, 14] The EAPC recommends the following strategies for managing general adverse effects associated with oral morphine:[13]

- reducing opioid dose,
- rotating opioids,
- changing the route of administration, and
- **symptomatic management.**

[11] Glare P, and Lickiss JN (1992). "Unrecognized constipation in patients with advanced cancer: a recipe for therapeutic disaster." J Pain Symptom Manage **7(6)**: 369-371.

[12] Pappagallo M (2001). "Incidence, prevalence, and management of opioid bowel dysfunction." Am J Surg **182**: 11S–18S.

[13] Hanks GW, Conno F, *et al* (2001). " Morphine and alternative opioids in cancer pain: the EAPC recommendations." Br J Cancer **84**: 587–593.

[14] Cherny N, Ripamonti C, *et al* (2001). "Strategies to manage the adverse effects of oral morphine: an evidence-based report." J Clin Oncol **19**: 2542–2554.

Importantly, each of these strategies has limited benefit for most patients with OIC. The obvious disadvantage of reducing opioid dose is that analgesia will be compromised, and severely impairs quality of life. Opioid rotation may serve to minimize other opioid induced side effects but does not appear to impact on constipation[15]. **Consequently, prevention of OIC and bowel dysfunction in general, is considered to be a more effective strategy than merely treating it when it occurs**.[8, 11] Experience from an Australian palliative care centre reporting on their practice based on 3,000 referrals, for predominantly cancer patients, over 6 years noted that:

*"…oral morphine doses in excess of 100-200 mg every 4 hours are extremely unusual, and often indicate that a factor, such as **undiagnosed fecal impaction**, is operating. In such cases, improved pain control occurs paradoxically in the context of decreasing morphine requirements once the exacerbating factor is relieved."*[11]

Therefore, the level of pain experienced by a patient is a combination of the primary pain source and the discomfort from constipation (on occasion with some complication). Once the latter is removed, the primary pain can be appropriately controlled, potentially with lower opioid doses. This also may explain why a proportion of patients that are switched from an opioid (due to their persistent constipation) sometimes report better pain management.

Simple laxatives are not an effective alternative treatment for Targin® tablets

Unlike Targin® tablets, pharmaceutical products currently used to manage opioid-induced constipation (OIC), such as over-the-counter (OTC) laxatives, do not address the underlying opioid receptor-mediated cause of constipation.

[8] Kurz A and Sessler DI (2003). "Opioid-induced bowel dysfunction pathophysiology and potential new therapies." Drugs Ageing **63(7)**: 649–671.

[11] Glare P and Lickiss JN (1992). "Unrecognized constipation in patients with advanced cancer: a recipe for therapeutic disaster." J Pain Symptom Manage **7(6)**: 369-371.

[15] McNicol E, Horowicz-Mehler N, *et al* (2003). "Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review." J Pain **4(5)**: 231-256.

Simple laxatives are often ineffective, unpredictable, have a potential for over-use and dependency (both psychological and physical), and are themselves associated with a range of side effects and are not without risks to patients.[8, 16] For example:

i) Senna and bisacodyl are stimulant laxatives commonly used to treat OIC. They frequently cause painful abdominal cramps whilst inducing, successfully or otherwise, laxation; additional pain that adds unnecessary burden and distress for patients already suffering chronic severe pain. **Moreover, the literature notes that chronic use can lead to melanosis coli, a condition that has been debated as a premalignant state**.

ii) Fibre bulking agents are also not considered useful for treating OIC. Indeed, debilitated patients with advanced illness associated with chronic pain e.g. advanced cancer are frequently in fluid deficit. **Administering fibre bulking agents to such patients is not recommended and can be hazardous, and exacerbate constipation**.

iii) Sugar based osmotic agents e.g. lactulose, sorbitol etc that increase fluid retention in the gastrointestinal tract are also associated with significant issues for chronic pain patients. Colonic bacteria hydrolyse the polysaccharide molecular bonds in these agents and metabolise the resultant monosaccharides, **producing gas that can lead to uncomfortable and painful bloating**.

iv) Non-pharmacological interventions e.g. increasing dietary fiber and fluid intake. Regular exercise and establishing a regular bowel routine are usually insufficient to prevent or treat opioid-induced bowel dysfunction, and most patients receiving long-term opioid therapy require pharmacological intervention.[12]

Routine ingestion of numerous pills or a large volume of liquid makes compliance difficult because chronic nausea, anorexia and dysphagia are common in this population.

Loss of bowel control is also often a significant issue. **When laxation interventions are successful, the time of laxation can be unpredictable and present personal and social dilemmas**.[17] When chronic pain patients take laxatives to treat the severe constipation caused by opioids, the results

[8] Kurz A and Sessler DI (2003). "Opioid-induced bowel dysfunction pathophysiology and potential new therapies." Drugs Ageing **63(7)**: 649–671.

[12] Pappagallo M (2001). "Incidence, prevalence, and management of opioid bowel dysfunction." Am J Surg **182**: 11S–18S.

[16] Reimer K, Hopp M *et al* (2009). "Meeting the challenges of opioid-induced constipation in chronic pain management – a novel approach." Pharmacology **83**:10–17.

[17] Thomas J (2008). "Opioid-induced bowel dysfunction." J Pain Symptom Manage **35(1)**: 103-113.

can be unpredictable. The person can lose control over their bowel movements, and this can be particularly embarrassing and distressing should this happen for instance when they are with family and friends at a BBQ.

Considering laxative use for constipation, considerably fewer patients receiving opioid therapy will achieve the desired treatment outcome compared with those in a normal survey population.[11] Despite the wealth of laxatives available to treat constipation, an estimated 54% of patients treated for OIBD do not achieve the 'desired result' with medication even half the time, whereas this was achieved in 84% of the general non-OIC population suffering from constipation.[11] Perhaps this limited efficacy should not be surprising in the context of the absence of treatments specifically designed for the treatment of OIBD.

A recent Cochrane review examining the use of laxative for palliative care patients with OIC found insufficient evidence regarding laxative efficacy and concluded that there was uncertainty as to the best management of constipation in this group of patients.[18]

How Targin® tablets improve on existing treatments

Contrary to the advice that appears to have been provided to Government by the Department of Health & Ageing (DoHA), the severe constipation that can be caused by strong opioid analgesics used to treat chronic severe pain is not a trivial condition as is now being claimed by Government. The cause and severity of constipation induced by opioid treatment is not the same as constipation experienced by most people in the community from time to time. An obvious consequence of this is that the approach to treatment of OIC – because of the separate and distinct causative factors – must also differ. That is, laxatives do not address the cause of OIC and consequently are a less than adequate treatment.

[8] Kurz A and Sessler DI (2003). "Opioid-induced bowel dysfunction pathophysiology and potential new therapies." Drugs Ageing **63(7)**: 649–671.

[12] Pappagallo M (2001). "Incidence, prevalence, and management of opioid bowel dysfunction." Am J Surg **182**: 11S–18S.

[18] Candy B, Jones L *et al* (2011). "Laxatives or methylnaltrexone for the management of constipation in palliative care patients (review)." *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD003448. DOI:10.1002/14651858.CD003448.pub3.

OIC is principally a peripheral effect mediated by opioid receptors in the GI tract[8] and, until now, it has been an elusive goal to separate this unwanted peripheral effect from the central analgesic effect. Targin® tablets are a novel approach for selectively and locally antagonising the gastrointestinal effects of opioids involving the co-administration of a μ-opioid receptor antagonist with negligible systemic availability, oral naloxone, with an opioid. Simply put, Targin® tablets are a strong opioid that treat Australians with chronic severe disabling pain with the additional benefit of helping to prevent and/or treat opioid induced constipation (OIC). Moreover;

i. By combining two different agents, oxycodone and naloxone, Mundipharma have been able to create a medicine that treats the chronic, severe pain and helps prevent the opioid induced constipation (associated with all opioid analgesics).
ii. Targin® tablets are <u>not</u> an opioid mixed with a laxative. Oxycodone is an opioid receptor agonist and naloxone is an opioid receptor antagonist (acting only in the gut). This results in the <u>prevention</u> of OIC at the receptor level in the gut rather than attempting to <u>cure</u> it symptomatically through significantly less reliable laxative treatment.
iii. There is no other strong opioid analgesic available to Australian patients which treats chronic severe disabling pain, whilst simultaneously addressing the cause of OIC and helping prevent it.

Reducing prescription opioid abuse

Of course, the issue of abuse and diversion of strong prescription opioids is a major concern for the community, the health profession, State and Federal regulators, law enforcement agencies and, indeed, Mundipharma. Moreover, the potential abuse deterrence characteristic of Targin® tablets was accepted as an important consideration in the PBS listing approval recommendation from PBAC.

It is therefore disappointing that Cabinet would take a decision to not immediately list on the PBS the only opioid analgesic in technology that would discourage addicts from abusing the opioid by both injection and the intranasal administration routes, combined with an important and innovative advance in treatment of chronic severe disabling pain. Whilst Targin® tablets may not be the complete answer to the important community concern of prescription opioid abuse; Mundipharma would submit that it's an important start.

The clinical need for Targin® tablets

Of course, implicit in the Government's indefinite PBS listing deferral of Targin® tablets, is the assertion that simple laxative treatment of OIC is an acceptable alternative. This is not the case. Briefly;

- Firstly, the evidence suggests there is a low rate of co-prescribing of laxatives in patients received prescriptions for opioids.
- Secondly, simple laxatives are often ineffective, unpredictable, have a potential for overuse and dependency, and are associated with a range of disturbing side effects.
- It is far better for patients if the OIC is prevented from occurring in the first place.

Reducing or avoiding the resultant cycle of compromised pain management and constipation is an important objective for improving the management of chronic, severe pain patients.
The PBS listing of Targin® tablets will provide an alternative to OxyContin® tablets alone or in conjunction with prophylactic laxatives. **With the listing of Targin® tablets on the PBS there is a substantive change in the treatment algorithm for patients suffering from chronic pain**. The commonly observed cycles of analgesia medication alteration and adjustment, with a view to alleviating the constipation cycle, is broken with the use of Targin® tablets.

No longer does constipation have to be an inevitable outcome of effective opioid analgesia.

This opportunity is already being realised in Germany where Targin® tablets has been available since 2006. Post-marketing experience has shown that only 3% of opioid naïve patients (treated with Targin® tablets) now receive prophylactic laxatives.

(C) Any consequences for the pharmaceutical sector of such deferrals;

Over several years, Mundipharma has diligently complied with the Government's extensive and detailed medicines registration and PBS reimbursement guidelines. On the basis of robust scientific and clinical data, the TGA has accepted that Targin® tablets are safe, efficacious and of acceptable quality. Similarly, the PBAC has determined that, on the basis of robust scientific, clinical and health economics data that Targin® tablets should be PBS listed and are cost-effective at a price subsequently approved by the PBS Pricing Section.

Conservatively, we estimate the local regulatory submissions ('user pay') costs to date of bringing this novel, new medicine to Australian patients to be well in excess of $1 million.

In order to provide the necessary guarantee of supply when a product is listed on the PBS, it is necessary for the sponsor to incur substantial costs. In good faith, and unaware that Cabinet was about to change the PBS listing rules without any discussion or prior warning, Mundipharma has imported a consignment stock of Targin® tablets of considerable value from the UK into Australia in order to meet this guarantee immediately upon PBS listing of this product.

It is not possible, under current PBS listing processes, to meet guarantee of supply obligations without pre-empting the listing date on receiving a positive recommendation from PBAC. We note that this stock, with limited shelf-life, is finished in dedicated packaging to comply with relevant Australian Therapeutic Goods Orders (TGO 69 and amendments) and State and Territory legislative requirements relating to labelling and Scheduling.

The stock of Targin® tablets currently held in store has been purchased from the manufacturer and cannot be returned to the manufacturer in the UK for repackaging and distribution to other markets.

Mundipharma contends that it was perfectly reasonable to expect the PBS listing of Targin® tablets to proceed following the PBAC's positive recommendation and agreement on price with the PBPA. This has been the process for at least a couple of decades, with the only exception to this that Mundipharma is aware of being Viagra tablets. Moreover, with the lengthy lead times and complex regulatory requirements for Controlled Drugs (Drugs of Addiction) to import product from the UK, it was necessary for Mundipharma to initiate importation at the earliest opportunity in order to meet Guarantee of Supply obligations.

Mundipharma now holds a significant volume of stock of Targin® tablets in our Sydney warehouse, which was imported in anticipation of PBS listing. The expiry dating for this stock is as follows:

i. Targin® 5/2.5mg tablets - expiry 31st December 2012
ii. Targin® 10/5mg tablets - expiry 30th November 2013
iii. Targin® 20/10mg tablets - expiry 30th November 2013
iv. Targin® 40/20mg tablets - expiry 30th November 2013

It is important to note that:

1) Pharmaceutical wholesalers will not generally accept stock of non-PBS listed items with less than 9 months shelf life remaining at the time of purchase. Thus, Mundipharma will be required to accept returned, unsold stock at product expiry, from wholesalers and this will have to be written-off as it is no longer saleable.
2) Additionally, the uptake of Targin® tablets in the marketplace will not be immediate. That is, upon PBS listing of Targin® tablets pharmacists will only order Targin® tablets from wholesalers once doctors begin writing prescriptions. There is always a significant time lag between what are called ex-factory sales (Mundipharma to wholesaler) and in-market sales (wholesaler to pharmacist). This means that even if Targin® tablets were PBS listed today, there will likely be significant stock of the 5/2.5mg tablets remaining in store 6 months before its expiry date that will be unsaleable and will have to be written-off (destroyed). Of course, the longer the delay to listing the greater the quantity of stock that will be subject to write-off and destruction.
3) Finally, as the three higher strengths of Targin tablets have longer expiry dating, it would not be appropriate to PBS list these in the absence of a listing of the lowest strength. This means, because of long order lead times, we will need to place an order for the 5/2.5mg strength with the UK manufacturer by 30th September 2011 if we are going to have saleable stock in Australia around the time that the existing stock becomes unsaleable (9 months before its 31st December 2012 expiry date i.e. 31st March 2012). Of course, Mundipharma would be cautious about placing any order for replacement stock without certainty around the PBS listing date.

As can be seen, the logistics around supplying Controlled Drugs on the PBS is complex. Whilst this may not be a concern for Cabinet, it does pose significant issues for Mundipharma in the absence of any certainty around the PBS listing process.

Mundipharma is now facing considerable financial loss as this stock, now sitting unused in our warehouse storage facility, will likely have to be destroyed should Cabinet not agree to list Targin® tablets on the PBS in the foreseeable future.

Clearly, Mundipharma would not have imported this level of stock had we received advanced notice the $10 million incremental cost to the PBS threshold requirement was to be abolished.

(D) Any impacts on the future availability of medicines in the Australian market due to such deferrals;

Mundipharma has not yet made any final decisions concerning future applications for the Pharmaceutical Benefits Scheme listing of products currently progressing through the TGA for registration. However, the current period of instability in the PBS listing approvals process will undoubtedly be a key consideration when assessing the viability of future applications. The current uncertainty and instability is not encouraging for the pharmaceutical industry in Australia, and is in direct conflict with the 4th pillar of Australia's National Medicines Policy (NMP)[19], of "maintaining a responsible and viable medicines industry". Mundipharma must inevitably treat all future interactions with Government departments cautiously in order to avoid financial penalties when changes in policies are implemented without consultation or prior warning.

(E) The criteria and advice used to determine medicines to be deferred

So far as Mundipharma is aware, the only rationale Government has to date provided underpinning the new policy change, for the Cabinet to defer the PBS listing of PBAC positive recommendations is if Cabinet has been advised that:

1. Alternative medications are presently available to patients, and
2. If the proposed listing was considered unaffordable to the Budget.

A PBAC recommendation based on cost-effectiveness criteria, by its very nature, indicates that the proposed new medicine offers some greater benefit than those medicines/therapies currently available.

The seven medicines and one vaccine deferred by Cabinet in February 2011 were:

- Botox (Allergan) Severe sweating;
- **Duodart (GSK) Enlarged prostate;**
- Invega sustenna (Janssen) Schizophrenia;
- Targin® (Mundipharma) Chronic disabling pain;
- Symbicort (AstraZeneca) Lung disease;
- Fragmin (Pfizer) Blood clots;
- Synarel (Pfizer) IVF treatment; and

[19] Australian Government, Department of Health & Ageing website: Accessed 14th July 2011. http://www.health.gov.au/internet/main/publishing.nsf/content/National+Medicines+Policy-1

- **Prevenar 13 catch-up (Pfizer) Pneumococcal vaccine.**

Of these, the Government announced on Budget night (10th May 2011) that it would list the Prevenar catch-up vaccine, and announced on 21st June 2011 that it would list Duodart. The other six remain deferred. Fragmin has subsequently been listed but for a new strength – that is, the February deferral still stands.

In addition, the PBAC made several positive recommendations at its March 2011 meeting with the following major submissions:

- Gilenya (Novartis) Multiple Sclerosis;
- **Revolade (GSK) Spontaneous internal bleeding;**
- **Tobi (Novartis) Antibiotic to treat infection related to cystic fibrosis;**
- Xeloda (Roche) Colon cancer;
- Pradaxa (Boehringer Ingelheim) anticoagulant;
- **Glivec (Novartis) Gastro-intestinal tumour; and**
- **Risperidone Consta (Janssen) Bipolar disorder.**

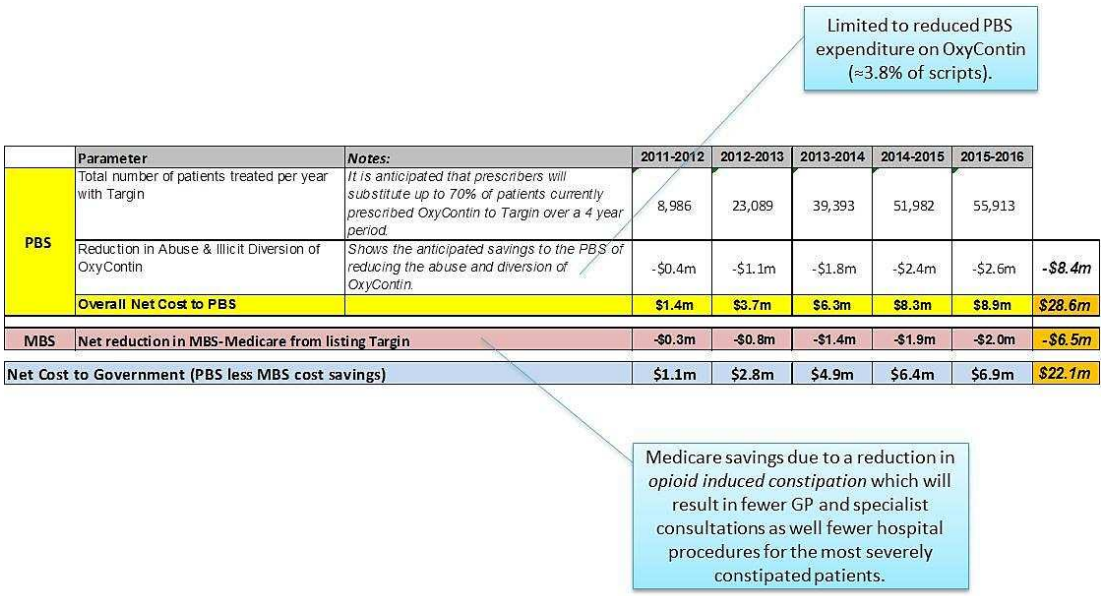
Of these, Government announced on 21st June 2011 that the following medicines would be listed: Revolade, Tobi, Glivec, Risperidone Consta; (Erbitux was also listed, but was recommended by PBAC in July last year).

Following an analysis of Cabinet decisions to either list or withhold medicines from the PBS, Mundipharma is still unable to understand the basis on which these decisions are being made. The decision to defer PBAC listing recommendations is unprecedented. The PBAC has determined that these new medicines offer significant clinical benefit and are cost-effective ('value for money') compared with other treatments or products for the same conditions.

The only insight Mundipharma has into the PBS listing criteria used by Cabinet has been provided by the Secretary of the Department of Health and Ageing, during the Senate Estimate Hearing of 31st May 2011, where it was acknowledged that **there are no formal criteria used by Cabinet to determine which medicines already recommended by the PBAC are PBS listed and which are not**.

(F) The financial impact on the Commonwealth Budget of deferring the listing of medicines;

The process of applying for the PBS listing of new medicines on the PBS requires detailed and complex calculations of estimated incremental costs to be provided to both the PBS and Government. This involves modelling various scenarios based on the best available evidence. The forward estimates are challenged and subject to the most rigorous scrutiny and review by the Drug Utilisation Subcommittee (DUSC) of DoHA. In the case of Targin® tablets, the following incremental costs were finalised/agreed with DUSC.



	Parameter	Notes:	2011-2012	2012-2013	2013-2014	2014-2015	2015-2016	
PBS	Total number of patients treated per year with Targin	*It is anticipated that prescribers will substitute up to 70% of patients currently prescribed OxyContin to Targin over a 4 year period.*	8,986	23,089	39,393	51,982	55,913	
	Reduction in Abuse & Illicit Diversion of OxyContin	*Shows the anticipated savings to the PBS of reducing the abuse and diversion of OxyContin.*	-$0.4m	-$1.1m	-$1.8m	-$2.4m	-$2.6m	*-$8.4m*
	Overall Net Cost to PBS		**$1.4m**	**$3.7m**	**$6.3m**	**$8.3m**	**$8.9m**	*$28.6m*
MBS	**Net reduction in MBS-Medicare from listing Targin**		**-$0.3m**	**-$0.8m**	**-$1.4m**	**-$1.9m**	**-$2.0m**	*-$6.5m*
Net Cost to Government (PBS less MBS cost savings)			**$1.1m**	**$2.8m**	**$4.9m**	**$6.4m**	**$6.9m**	*$22.1m*

The Government has indicated its intention to bring the Federal budget back into surplus in 2012-13. However, as can be seen from the schematic above the best estimate of the incremental cost to Government, closely reviewed and agreed with the DUSC, following the 1st year of listing of Targin® tablets is just $1.1 million and $2.8 million in year two (2). Moreover, the estimated incremental cost to the PBS in year five (5) is < $10 million (at $8.9 million). Mundipharma would strongly contend that in the context of the Federal budget **the immediate PBS listing of Targin® tablets would not pose any threat to Government achieving its stated goal**. This is even more so, as discounting the cost to Government of PBS listing Targin® tablets, for the listing delay already incurred would make the incremental cost to Government even lower – if not cost neutral – for the critical fiscal years of concern to Government.

Of course, the incremental health benefit to tens of thousands of chronic severe pain patients of the PBS listing of Targin® tablets, at immaterial cost within the context of the Federal budget, is very significant.

(G) The consultation process prior to the deferral;

Mundipharma is disappointed at the lack of consultation with the Company prior, or indeed subsequent, to this important adverse Government decision being taken. Importantly, Mundipharma was only advised of this decision by telephone from DoHA late on Thursday 24th February 2011, the day prior to the Minister's Media Release statement on this matter on Friday 25th February 2011.

Until that time, Mundipharma was given every reason to believe the process for the listing of Targin® tablets was proceeding on track according to normal Departmental processes. Had earlier advice been received, issues around the importation from the UK of stock of considerable value and consequent associated financial loss to Mundipharma could obviously been avoided.

(H) Compliance with the intent of the Memorandum of Understanding signed with Medicines Australia in May 2010;

Mundipharma notes that the pharmaceutical industry has, over the last seven years, responded to every call by government to assist in ensuring the future sustainability of the PBS by delivering substantial savings through a range of policy measures. The most recent of these was through the Memorandum of Understanding (MoU) signed last year, with savings measures legislated in November 2010. These recent measures will deliver an additional $1.9 billion in savings – savings designed, at least in part, to ensure 'headroom' is available for the listing of new, innovative medicines such as Targin® tablets.

The underlying premise for the signing of the MoU was to provide 'certainty' for the pharmaceutical industry. The very fact that 'certainty' no longer exists is clear evidence the intent of the MoU has been undermined by the decision to defer medicines from PBS listing.

It is disappointing therefore, particularly to chronic severe pain patients, that just a very small fraction of these savings cannot be utilised to the significant benefit of these long-suffering chronic pain patients in Australia. Mundipharma appreciates the fiscal constraints in which the Government must currently operate, but we strongly believe that this should not be at the expense of members of the community who are most vulnerable.

(I) Any other related matter.

Reduced abuse potential of Targin® tablets – an added benefit

The abuse and diversion of prescription opioid medicines in the community is a problem acknowledged by many, but without a clear solution.

A recent report by the Australian Crime Commission[20] identified that 32% of injecting drug users reported use of illicitly obtained oxycodone. The report, however, provided no recommendations to reduce this abuse. Further, the Minister for Human Services on 6th March 2011[21] announced an investigation into fifty (50) doctors for the inappropriate prescribing of oxycodone.

While supporting this investigation, Mundipharma believes the availability of Targin® tablets will be an important first step into reducing abuse and diversion. The incorporation of naloxone (opioid receptor antagonist) into Targin® tablets has been acknowledged by leading clinicians as potentially discouraging abuse and diversion of this strong opioid analgesic.

An addict seeking to misuse Targin® tablets parenterally (by injection) or intranasally (crushing and 'snorting') will likely experience most unpleasant opioid withdrawal symptoms.

Targin® tablets are the only opioid analgesic giving General Practitioners the ability to assess the *bona fides* of patients seeking opioid treatment in their daily practices. A patient refusing treatment with Targin® tablets and pressing for an alternative strong opioid analgesic can be considered suspect and attempting procure prescription opioid for their personal use, or for diversion into the illicit drug market. Such patients warrant further clinical assessment for prescription or illicit drug abuse and, if appropriate, encouragement to seek assistance from specialist Drug & Alcohol services.

The issue of abuse and diversion of prescription opioids is a major concern for the community, the health profession, State and Federal regulators, law enforcement agencies and, indeed, Mundipharma. It is incomprehensible that Cabinet would delay the PBS listing of the first opioid analgesic that incorporates this abuse deterrence technology. The decision is certainly not in the

[20] Australian Crime Commission website. "Organised Crime in Australia Report (2011). Accessed on 14th July 2011 http://www.crimecommission.gov.au/publications/oca/index.htm

[21] Minister for Human Services website: http://www.mhs.gov.au/media/media_releases/2011/03/6_march_2011_-_doctors_targeted_for_over_-_prescribing_narcotics.php

best interests of the community, fearful of the increased abuse and diversion of prescription opioid analgesics throughout Australia.

The potential abuse deterrence characteristic of Targin® tablets was accepted by PBAC as an important consideration in the PBS listing approval recommendation. The PBAC evaluation suggested that the rate of such opioid abuse and re-direction is likely to be around 3.8% (based on AIHW findings). The potential for Targin® tablets to be similarly misused is likely to be negligible given that if used via the parenteral or intranasal routes of administration Targin® tablets will induce opioid withdrawal symptoms.

Attachment 1 - Current membership of the Pharmaceutical Benefits Advisory Committee (PBAC):

Emeritus Professor Lloyd Sansom AO (Chair) is the former Head of School of Pharmacy and Medical Sciences at the University of South Australia. He has been Chair of the PBAC since 2001.

Dr John Bennett is a general practitioner and Practice Principal of the University Health Service at the University of Queensland. He is also a casual lecturer and tutor in Epidemiology, Public Health, Evidence Based Medicine, Medical Informatics and Primary Care Medical School at University Of Queensland.

Dr Jim Buttery is Research Development Director, NHMRC Centre for Clinical Research Excellence in Child and Adolescent Immunisation and a consultant paediatrician and Infectious disease physician and the Royal Children's Hospital, Victoria.

Professor Terry Campbell is Professor of Medicine at University of New South Wales and Head of the Department of Medicine, St Vincent's Hospital, Sydney.

Associate Professor Michael Coory is Public Health Physician and Clinical Epidemiologist at the Murdoch Childrens Research Institute and Adjunct Associate Professor at School of Population Health at University of Queensland and University of Melbourne.

Dr Matthew Doogue is a Clinical Pharmacologist and Endocrinologist at Southern Adelaide Health Services and Flinders University School of Medicine, South Australia.

Professor Jennifer Doust is Professor of Clinical Epidemiology in the Centre for Research in Evidence Based Practice at Bond University and is a general practitioner in Brisbane.

Professor David Isaacs is Clinical Professor at the University of Sydney. He is a paediatrician at the Department of Infectious Diseases and Microbiology, based at The Children's Hospital at Westmead in Sydney.

Professor David G LeCouteur is a geriatrician, clinical pharmacologist and general physician. He is Professor of Geriatric Medicine at the University of Sydney, Director of the Centre for Education and

Research on Ageing (CERA), Director of the Biogerontology Laboratory of the ANZAC Research Institute and Senior Staff Specialist Physician at the Concord RG Hospital in Sydney. He is Chair of the PBAC Drugs Utilisation Sub-Committee.

Professor Geoff McColl is a rheumatologist and Professor of Medical Education and Training in the Melbourne Medical School at the University of Melbourne.

Mr Mitchell Messer has been a health consumer advocate for over 30 years and is the consumer member on the PBAC.

Dr Karen Peachey is a community pharmacist from Queensland with an interest in eHealth, pharmacoepidemiology and aged care.

Professor Andrew Roberts is a Clinical Haematologist at the Royal Melbourne Hospital and an NHMRC Practitioner Fellow and Head of Clinical Translation at The Walter and Eliza Hall Institute of Medical Research.

Dr Roger Sexton is a rural general practitioner and part time medical tutor at Adelaide and Flinders Universities. He has experience in procedural rural medicine, medical education and medical regulation. His special interests include doctors' health, dermatology and teaching.

Dr Rashmi Sharma is a general practitioner and Practice Principal of a large teaching practice in Canberra where she supervises nursing and medical students, interns and GP registrars. She is a Senior Lecturer at the ANU Medical School and President of the ACT Division of General Practice. She is a board member and medical educator for the regional general practice training provider, Coast City Country GP Training Ltd.

Associate Professor Rosalie Viney is a health economist at the Centre for Health Economics Research and Evaluation, University of Technology, Sydney. She is Chair of the PBAC Economics Sub-Committee.

Professor Robyn Ward is the Clinical Associate Dean at Prince of Wales Clinical School, UNSW, and Director of Cancer Services for South Eastern Sydney and Illawarra Local Health Networks. She is a

practising medical oncologist and a medical researcher.

Dr Frances Wilson is Senior Staff Specialist in Psychiatry and Clinical Director, Adult Psychiatry Unit at Westmead Hospital. She is a Clinical Senior Lecturer at Sydney University.

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