Submission to the Medicines Classification Committee for Reclassification of a Medicine

Classification of Paracetamol in modified release tablets containing 665 mg or less as a Pharmacy-only Medicine

Volume 1 of 1

Pages 1 - 103

SmithKline Beecham (New Zealand) Ltd
(trading as GlaxoSmithKline)

July 2001

Commercial-in-Confidence

Details of company making submission:

Street Address:

SmithKline Beecham (New Zealand) Ltd
(trading as GlaxoSmithKline)
6A Pacific Rise
MT WELLINGTON AUCKLAND

Postal Address:

SmithKline Beecham (New Zealand) Ltd
(trading as GlaxoSmithKline)
PO Box 62-043
SYLVIA PARK AUCKLAND 6

Contact Details:

Peter Thanopoulos
Senior Scientific Affairs Associate
GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue (Locked Bag 3)
ERMINGTON NSW 2115
AUSTRALIA

Phone: (+61 2) 9684 0988
Fax: (+61 2) 9684 1018
E-mail:peter.2.thanopoulos@gsk.com

TABLE OF CONTENTS

Introduction

PANADOL EXTEND is a novel modified release formulation of paracetamol. It is a bi-layer tablet containing paracetamol 665 mg, one layer containing immediate release (IR) paracetamol (31%) and the second layer containing sustained release (SR) paracetamol (69%). The recommended dosage is two 665 mg tablets (1.33 g) t.i.d. with a maximum daily dose of six tablets (3.99 g). These proportions result in a dissolution profile which releases paracetamol to give plasma levels adequate for analgesic relief for up to 8 hours. It is anticipated that the extended duration of action, compared with conventional dosage forms, will provide patients with a more convenient product, especially for use in conditions that require dosing for more persistent pain.

The Expert Report on the Clinical Documentation (UK CER) [Attachment 1] which accompanies the submission evaluates the clinical data which justify approval of PANADOL EXTEND with regard to the proposed indications. It presents the data that show that PANADOL EXTEND at the recommended dosage of two 665 mg tablets (1.33 g) t.i.d. is therapeutically equivalent to two PANADOL 500 mg tablets (1 g) q.i.d. PANADOL EXTEND is bioequivalent to PANADOL in the extent of absorption of paracetamol. Clinical equivalence has been demonstrated between PANADOL EXTEND and PANADOL in patients with pain associated with osteoarthritis and in patients with acute post-surgical dental pain. A review of the available efficacy and safety data for paracetamol, including other modified release forms, has not identified any issue that would preclude approval of the product.

The maximum daily dosage (MDD) of 4000 mg for PANADOL remains unchanged for PANADOL EXTEND.

This medicines classification submission seeks to change the scheduling of PANADOL EXTEND from a Prescription Medicine to that of a Pharmacy-only Medicine. Such a change would also harmonise the scheduling of PANADOL EXTEND with that currently in place in Australia.

PART A

1. International Non-proprietary Name (or BAN or USAN) of the medicine

INN: Paracetamol
BAN: Paracetamol

2. Proprietary Names

PANADOL® EXTEND™ a modified release medicine containing 665mg of paracetamol per tablet.

3. Name of company/organisation/individual requesting reclassification

Street Address:
SmithKline Beecham (New Zealand) Ltd
(trading as GlaxoSmithKline)
6A Pacific Rise
MT WELLINGTON AUCKLAND

Postal Address
SmithKline Beecham (New Zealand) Ltd
(trading as GlaxoSmithKline)
PO Box 62-043
SYLVIA PARK AUCKLAND 6

4. Dose form(s) and strength(s) for which a change is sought

Modified release tablets containing paracetamol 665mg per tablet.

5. Pack size and other qualifications

Pack sizes: 6 tablets (pharmacy-only medicine) [physician sample pack].
18 tablets (pharmacy-only medicine)
36 tablets (pharmacy-only medicine)

6. Indications for which change is sought

Change is sought for all existing paracetamol indications. These indications fall under the two broad categories Analgesia (relief of pain symptoms) and Antipyresis (fever reduction).

7. Present classification of medicine

Prescription medicine – Paracetamol in tablets or capsules containing more than 500 milligrams per dose unit.

8. Classification sought

Pharmacy-only medicine – Paracetamol in modified release tablets containing 665 milligrams or less.

9. Classification status in other countries (USA, Canada, Australia, and UK,)

9.1 USA: OTC medicine

A modified release paracetamol formulation has been available OTC in the USA as TYLENOL® Extended Relief or TYLENOL® Arthritis Extended Relief (McNeil Consumer Healthcare) having been launched there in 1994.

9.2 Canada OTC medicine

A modified release paracetamol formulation has been available OTC in Canada as TYLENOL® Arthritis Pain Extended Relief (McNeil Consumer Healthcare) having been launched there in December 1999.

9.3 AUSTRALIA: Pharmacy Medicine

The Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) states that paracetamol for therapeutic use is a Schedule 2 drug (Pharmacy Medicine).

9.4 UK: Status to be determined

An application has recently been submitted in the UK to market PANADOL EXTEND under the supervision of a pharmacist by requesting it be classified as a *P* status medicine. It has been requested that the Prescription Only Medicines (Human Use) Order 1997(SI1830), be further amended to grant an exemption for the maximum strength of 665 mg of paracetamol in the case of a tablet as a prolonged release formulation. The maximum daily dosage (MDD) of 4000 mg remains unchanged for this dosage form.

10. Extent of usage in NZ and elsewhere (e.g. sales volumes) and dates of original consent to distribute

10.1 New Zealand

The New Zealand Regulatory Guidelines for Medicines (NZRGM, 4th Edition, 2000) in section 10.3.5 – Paracetamol state that "*solid dose forms for adults should be multiples of 250 mg or 500 mg only*". Based on this information and advice from the Medsafe Evaluation section [Attachment 2] no application for registration of PANADOL EXTEND has been submitted to-date. Without classification of this modified release 665 mg tablet so that the NZRGM may be revised, an application to register PANADOL EXTEND would prove difficult.

Consequently, no sales data is available for PANADOL EXTEND as the medicine has not yet been marketed in New Zealand. However, is forecast that PANADOL EXTEND would account for approximately 2.5% of total PANADOL sales over a calender year (3.5 million tablets), if available as a Pharmacy-only medicine.

Sales data for regular PANADOL (500 mg tablets) in calender year 1999 was approximately 142 million tablets (inclusive of PHARMAC contracts).

10.2 Australia

PANADOL EXTEND was evaluated and approved by the TGA OTC Medicines Evaluation Section on May 25, 2001. The product began being marketed on June 15, 2001.

Consequently, no reliable sales data is available for PANADOL EXTEND as the medicine has not been marketed in Australia for any significantly measurable period of time. However, it is forecast that PANADOL EXTEND would account for approximately 5% of total PANADOL sales over a calender year (30 million tablets), when available.

Sales data for regular PANADOL (500 mg tablets) in calender year 1999 was approximately 600 million tablets.

10.3 Canada

A modified release paracetamol formulation has been available OTC in Canada since December 1999. TYLENOL® Arthritis Pain Extended Relief is a 650 mg paracetamol per tablet (50% immediate release 50% sustained release formulation) (McNeil Consumer Healthcare). It is available in packs of 50 or 100 tablets.

No Canadian sales data was available for TYLENOL® Arthritis Pain Extended Relief.

10.4 USA

A modified release paracetamol formulation has been available OTC in the USA since 1994. TYLENOL® Extended Relief or TYLENOL® Arthritis Extended Relief is a 650 mg paracetamol per tablet (50% immediate release 50% sustained release formulation) (McNeil Consumer Healthcare). It is available in packs of 24, 50 or 100 tablets.

No US sales data was available for TYLENOL® Extended Relief.

11. Labelling or draft labelling for the proposed new presentation(s)

Draft label copy for PANADOL EXTEND is provided as Attachment 3.

PANADOL EXTEND will be supplied in a blister pack comprising a laminate of clear Polyvinylchloride (PVC) coated with Polyvinylidene chloride (PVDC) sealed to a distinctive aluminium foil lid. The blisters are packed in cardboard cartons each containing 6,18 or 36 tablets. The cardboard carton's ends are safety sealed with tamper evident tape. Further, the entire carton is over-wrapped in a clear wrap whose ends are fused to provide an additional tamper evident barrier.

The proposed PANADOL EXTEND carton and blister strip are a distinctive shape that clearly differentiates them from regular PANADOL tablets. They are twice the height of existing PANADOL packs providing a much squarer and visibly different pack shape. Additionally, the PANADOL EXTEND pack employs a glossy foil finish to further distinguish it from regular Panadol. The packs of both regular Panadol and PANADOL EXTEND are provided as Attachment 4 to highlight the differences in pack size and graphics.

12. Proposed warning statements if applicable

12.1 Label

Doses should be equally spaced throughout the day.

PANADOL EXTEND should not be taken more frequently than every 6 hours. Can be taken with or without food. Not recommended for Children under 12 years of age. Should not be used with other paracetamol containing products.

CAUTION: This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful. If pain or symptoms persist, seek medical advice. Do not give to children below the stated age group except on medical advice.

12.2 Product Information Leaflet (PIL)

No PIL is proposed to be provided as a package insert in packs of PANADOL EXTEND.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

PANADOL EXTEND is a unique product as it is the first combination IR/SR paracetamol analgesic to be submitted for registration in Australia for the temporary relief of mild to moderate pain. Based on the outcome of this submission similar registration would be sought in New Zealand.

Based on this uniqueness it is expected that the entries for Paracetamol in Part I – Prescription medicines and Part III – Pharmacy-only medicines of the First Schedule of the Medicines Regulations 1984 would require amendment. The necessary amendments would not be expected to adversely affect the existing entires for Paracetamol.

Part B - Reasons for requesting classification change.

1. A statement of the benefits to both the consumer and to the public expected from the proposed change

PANADOL EXTEND tablets have been formulated for use in patients with mild to moderate pain and for the relief of fever as for PANADOL tablets. PANADOL EXTEND is a bi-layer tablet containing 665 mg paracetamol, one layer containing immediate release (IR) paracetamol (31%) and the second layer containing sustained release (SR) paracetamol (69%), which is designed to give analgesia for up to 8 hours after dosing following a single dose (2 x 665 mg). These proportions result in a dissolution profile which releases paracetamol to give plasma levels adequate for analgesic relief for up to 8 hours. It is anticipated that the extended duration of action compared with conventional dosage forms, will provide patients with a more convenient product, especially for use in conditions that require dosing for persistent pain.

As confirmed in two clinical trials, PANADOL EXTEND (1.33 g tid) and PANADOL Tablets (1 g qid) were therapeutically equivalent after 7 days treatment of pain due to osteoarthritis (OA) of the knee and, by implication, other painful conditions involving persistent pain where paracetamol is regarded as effective. A three times daily dosing regimen is more convenient for patients requiring repeat doses and has the potential to improve patient compliance and control of pain, compared with an immediate release paracetamol formulation administered four times daily. The advantage of a longer duration of action with PANADOL EXTEND is particularly important for the treatment of longer-lasting pain because patients will benefit from a reduced dose frequency.

A single dose of PANADOL EXTEND provided analgesia for up to 8 hours. Such patients would also benefit from the advantage of a longer duration of action with PANADOL EXTEND which applies to fever and acute pain indications where treatment with a single dose may be adequate. There may also be a possible reduction in the prescribing of more potent medications.

The toxicity profile of paracetamol when used as directed makes it suitable for self-treatment by the consumer. PANADOL EXTEND is an alternative to the use of IR paracetamol products in patients who would benefit from using an analgesic with a longer duration of action.

Pain sufferers need to have access to a product that can potentially relieve their pain for a longer period of time. PANADOL EXTEND available as a Pharmacy-only medicine will make such a product more accessible to patients.

2. Ease of self-diagnosis for the condition indicated

Extensive experience with other non-prescription analgesics used for similar indications demonstrates that it is highly unlikely that the use of PANADOL EXTEND would mask a significant underlying condition that required medical supervision.

A pharmacist or physician does not normally identify the need for symptomatic relief in the proposed indications. These conditions are routinely self-diagnosed and self-treated by the general public. The symptoms are treated by a variety of medications such as paracetamol, aspirin, and ibuprofen, which are available as pharmacy-only medicines or general sales medicines. Patients are clearly told on the label when to seek medical advice. There is no reason to believe there will be any greater risk associated with the use of PANADOL EXTEND compared to IR paracetamol or other analgesics available 'over the counter' (including sustained release formulations of ibuprofen available in the UK).

There is no reason to believe that the longer half-life of PANADOL EXTEND compared to IR paracetamol will increase the risk.

The patient should be able to make an accurate self-assessment of their condition. As discussed above, the proposed indications are routinely self-diagnosed without recourse to medical advice. There are few risks associated with such a practice. In those cases where symptoms do not improve or get worse, patients would normally resort to seeking medical advice and are advised to do so on the product label. The precautions and warnings should be clearly understood.

The company believes that PANADOL EXTEND when used as directed is suitable for self-treatment of the afore-mentioned minor ailments capable of being monitored by the consumer. There is no reason to believe that there will be any greater risk associated with the use of PANADOL EXTEND compared to IR paracetamol or other 'over the counter' analgesics.

3. Relevant comparative data for like compounds.

NUROFEN® Long Lasting tablets which each contain 300 mg of ibuprofen in a sustained release formulation where launched in the United Kingdom in May 1999 as a Pharmacy-only Medicine. A dose of up to 4 tablets can be taken in 24 hours (1200 mg). The product is available in packs of 12 or 24 tablets.

4. Local data or special considerations relating to NZ

Local data has been supplied in the specific sections throughout this submission. No additional local data has been supplied in this section.

5. Interactions with other medicines

There are no interactions with commonly used medications that could produce serious adverse reactions [1, 2]. Prolonged regular use of paracetamol may enhance the effect of coumarins but the findings are inconsistent [3]. Paracetamol is the analgesic of choice in patients receiving warfarin and short term use of paracetamol should not pose a hazard in these patients [3]. A SR formulation like PANADOL EXTEND makes no difference to these interactions.

Interactions are consistent with the existing PANADOL Tablets. The PANADOL EXTEND formulation does not raise additional concerns of potential drug interactions in comparison with IR paracetamol formulations.

6. Contraindications

Contraindications and precautions are consistent with those for PANADOL Tablets. The PANADOL EXTEND formulation does not raise additional concerns of potential contraindications in comparison with IR paracetamol formulations.

7. Possible resistance

This section is not applicable or relevant to this submission.

8. Adverse events - nature, frequency etc.

Reports or adverse reactions to paracetamol are rare. Although the following adverse reactions have been reported, a causal relationship to the administration of paracetamol has neither been confirmed nor refuted: dyspepsia, nausea, allergic and haematological reactions.

As discussed in the UK CER [Attachment 1, see Section 5.0]. paracetamol is exceptionally safe at therapeutic doses and there is a very low risk of either serious expected or serious unexpected adverse events. There has been very extensive use of paracetamol as a non-prescription medication in a large number of countries world-wide over the last 30 years.

The safety data from the four clinical studies with PANADOL EXTEND have shown that this product has a similar safety profile to IR paracetamol (see Section 5.2 of UK CER). The number of patients (1111 in total) recruited into these studies was relatively small in terms of assessing safety data, particularly for less frequent events. However, given the similar extent of absorption between PANADOL EXTEND and Panadol and the lower C_{max} associated with the former, it is entirely reasonable to conclude that the safety profile for PANADOL EXTEND will not differ significantly from that of IR paracetamol.

9. Potential for abuse or misuse.

9.1 Extremely low abuse potential

Paracetamol is not associated with dependence or addiction. There is no data to suggest a problem with abuse or misuse.

9.2 Low potential for harm from inappropriate use

In the event that a patient took PANADOL EXTEND qid in error instead of tid, the dose of paracetamol ingested over a 24 hour period would be 5.32 g rather than the standard dose of 4 g for IR paracetamol. This is still substantially less than 10–15 g paracetamol, which is considered to be potentially hepatotoxic when taken as a single dose by an adult [4, 5]. A daily paracetamol dose of less than 6 g is unlikely to saturate the safe pathways of elimination (glucuronidation and sulphation), and even then, glutathione reserves in the liver are likely to be adequate to detoxify NAPQI which is generated.

The distinctive package labelling and shape of the blister packaging should also assist in reducing this risk.

9.3 Prolonged Use

Patients are unlikely to use the product for prolonged periods of time without medical supervision. The conditions being treated usually improve in a short period of time. As noted above, if the condition deteriorates or persists patients are likely to seek pharmacist or medical advice as directed in the product label. Although there are risks associated with the prolonged use, as with any product, in practice these risks are extremely small and should be no greater with PANADOL EXTEND than with IR paracetamol or other the alternative therapy available as a pharmacy-only medicine for similar indications.

9.4 Overdose

9.4.1 Deliberate Overdose

Deliberate overdose with paracetamol does pose a significant medical problem because of the resultant hepatotoxicity. In considering this change to the classification of paracetamol, the risks associated with overdose of PANADOL EXTEND are the most significant issue that must be addressed. However, a review of the available data demonstrate that the risks associated with overdose of PANADOL EXTEND are highly unlikely to be any greater than those associated with overdose of IR paracetamol.

There is no reason to believe that the availability of PANADOL EXTEND as a non-prescription product will increase the frequency of overdose with paracetamol. Paracetamol is so widely available that a new formulation is unlikely increase availability further.

However, there are two specific issues to be addressed. First, whether the sustained release characteristics alter the current treatment guidelines. Second, if these guidelines are modified, are there any implications if the patient is mistreated i.e. treated as a case of IR paracetamol overdose rather than one of sustained release paracetamol. The issue of overdose with PANADOL EXTEND is also considered in the UK CER (see Section 5.4).

9.4.2 General Considerations

The hepatotoxicty of paracetamol in overdose is related to the formation of a toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI) which is normally detoxified by binding to glutathione in the liver to form cysteine and mercapturate derivatives [6, 7]. In an overdose situation, glutathione is depleted and the excess NAPQI binds irreversibly with liver cell proteins to cause hepatic necrosis. Treatment with agents which replete hepatic glutathione stores, such as *N*-acetylcysteine (NAC), the treatment of choice, prevents liver damage provided the patient is treated early enough.

The minimum single hepatotoxic dose of paracetamol is estimated to be 150 mg/kg or about 10 g. However, this is a very conservative estimate and in the majority of cases the dose would be much higher [7]. In cases of uncomplicated IR paracetamol overdose, reliable potential hepatotoxicity estimates can be obtained from a single plasma paracetamol level provided it is taken at a minimum of 4 hours after dosing [7]. Patients with levels above a treatment line joining plots on a semilogarithmic graph of 200 mg/L at 4 hours and 30 mg/L at 15 hours should be treated [6, 7]. This normal treatment line was derived from the experience of thousands of patients following IR paracetamol overdose at a time no treatment was available [7]. In certain high risk groups, e.g. those on enzyme inducing drugs, malnourished, a lower plasma paracetamol level (100 mg/L at 4 hours) is used as the treatment nomogram. These nomograms form the basis for treatment in the UK [8]. Other countries may use a different nomogram e.g. in the USA patients with plasma paracetamol levels above 150 mg/L at 4 hours post-ingestion receive oral NAC [9].

9.4.3 Treatment Guidelines for PANADOL EXTEND Overdose

There is no reason *per se* to believe that PANADOL EXTEND in overdose will be any more hepatotoxic than equivalent doses of IR paracetamol. During the initial period following ingestion, the systemic absorption of a sustained release formulation will in fact be lower than that of an IR formulation [10] as has been demonstrated for PANADOL EXTEND [see UK CER Section 3.3]. Potentially this could reduce the hepatotoxicity of sustained release formulations since the rate of NAPQI production may be reduced [10]. Certainly, there are data to suggest a reduced hepatotoxicity in cases where paracetamol absorption is delayed due to concomitant ingestion of other drugs delaying gastro-intestinal motility [11-13]. Whether this applies in the case of delayed absorption with SR paracetamol is unclear and it is prudent to assume that the risk of hepatotoxicity following overdose with PANADOL EXTEND is similar to that of equivalent doses of paracetamol. In that respect, use of the treatment nomogram is appropriate and patients with plasma paracetamol levels above the appropriate line at four or more hours should receive NAC.

However, the key difference between PANADOL EXTEND and IR paracetamol is delayed absorption with an increase in T_{max} [see UK CER Section 3.3]. Following IR paracetamol, absorption is normally complete by 4 hours post-ingestion. Theoretically, with sustained release formulations, absorption may continue after four hours with a resultant increase in plasma levels. There is the possibility that patients with plasma paracetamol levels below the normal treatment line subsequently have levels above the line. It is therefore recommended that in the case of overdose with PANADOL EXTEND that an additional plasma paracetamol level is determined 4-6 hours after the first. Since the antidotal efficacy of NAC decreases with time, it is important that treatment is not delayed [7]. In those cases of PANADOL EXTEND overdose where plasma paracetamol levels is close to or falls above the high-risk treatment line, treatment should be begun immediately. Treatment can subsequently be stopped in those cases where a repeat determination demonstrates levels are below the normal treatment line. This recommendation may lead to overtreatment compared to current guidelines but it is better to over-treat than under-treat. Apart from the very occasional case of hypersensitivity reaction, NAC is extremely well-tolerated. In those cases with hypersensitivity, stopping the infusion can normally be restarted without problems once the reaction has settled [8]. The company are preparing revised 'Guidelines for the Management of Paracetamol Overdose' which will incorporate necessary information on PANADOL EXTEND. These guidelines will be issued prior to marketing of PANADOL EXTEND to all public and private hospitals, Poisons Information Centres and other key healthcare specialists in New Zealand to ensure the appropriate information is made available to those treating paracetamol overdose.

There is experience in the USA with a sustained released paracetamol, Tylenol Extended Relief or Tylenol Arthritis Extended Relief (McNeil Consumer Healthcare), which has been available as a non-prescription product since 1994. The above guidelines are consistent with the recommendations by McNeil for the treatment of sustained release paracetamol.

Experience in the USA would suggest that these modified treatment recommendations are indeed being cautious [10]. Several case reports of overdose with Tylenol Extended Relief have been published in the literature [14-17]. There have been no fatalities reported. Indeed Dr Richard Dart, Director of the Rocky Mountain Poison and Drug Centre and co-author of the largest series reviewing overdose cases of SR paracetamol [17] is not aware of any cases of fulminant hepatic failure or death associated with SR paracetamol in the USA [Personal Communication, Attachment 5]. There is one published case in which there was a delayed, second plasma paracetamol peak [15]. However, this patient had also other medication (including a combination product containing dextromethorphan) which may have delayed absorption. It is well recognised that co-ingestion of drugs affecting absorption may delay absorption of even IR paracetamol and present difficulties in the use of the treatment nomogram [7, 10, 18].

Cetaruk and co-workers review 13 cases of overdose of Tylenol Extended Relief [17]. The amount of paracetamol ingested varied from 10.4 to 65 g. Nine patients received partial or complete courses of NAC. No patient developed evidence of liver damage. Eight patients had prolonged elimination phase for paracetamol suggesting drug absorption continued beyond 2-4 hours. There were three patients who had plasma paracetamol levels below the USA treatment line that later had levels above the line. However, a review of the data presented graphically [17 see Figure], would suggest that peak plasma levels were observed in all patients by 4 hours post-ingestion. In two of the three patients in which the plasma paracetamol level subsequently increased above the US treatment line, it would appear that the paracetamol levels did not cross the normal UK treatment line, which is higher than the US treatment line. In the third patient, the paracetamol level did go above the normal UK treatment line. Although these data would suggest that peak paracetamol levels will be achieved within four hours following overdose with SR paracetamol, it is important to note that PANADOL EXTEND contains a mixture of IR paracetamol 31% and SR paracetamol 69%. Tylenol Extended Relief contains a 50:50 ratio of IR and SR paracetamol. Absorption of paracetamol may be more prolonged with PANADOL EXTEND than Tylenol Extended Relief. In interpreting the safety data from the USA, it is also important to note that treatment with NAC is initiated at lower paracetamol levels than in the UK (plots from 150 mg/L at 4 hours compared to 200 mg/L).

The UK CER (see Section 5.1.1) presents details of a patient from Denmark who died of fulminant hepatic failure following an overdose of Panodil Retard [19]. This is a SR paracetamol formulation containing 1 g of paracetamol with a dissolution rate far slower than PANADOL EXTEND. NAC treatment had been initiated following admission to hospital. However, the treatment was discontinued after 5 hours when the plasma paracetamol level was found to be below the treatment line. The patient had in fact taken two overdoses of SR paracetamol 24 hours apart together with other medication including phenobarbitone. The treatment nomogram for paracetamol was devised to treat cases of single overdoses of paracetamol and cannot be interpreted when multiple overdoses or staggered overdoses are taken. The relative safety of SR paracetamol and appropriate treatment procedures cannot be assessed from this case.

9.4.4 Risk of Mistreatment

There is a possibility that patients who take an overdose of PANADOL EXTEND are treated on the basis that they have taken an overdose of the standard IR paracetamol rather than SR paracetamol. This could have clinical consequences in a patient whose plasma paracetamol level is below the normal treatment line and is not treated based on the current guidelines for IR paracetamol but whose levels subsequently rise above the line. However, in my view the risk of this occurring is extremely small for the following reasons.

First, the both the carton and blister pack for PANADOL EXTEND will be a different shape than regular PANADOL. This distinctive packaging will aid recognition for both the patient and the healthcare professionals involved in the management of the case. Additionally, the tablet will be marked with the logo "8". These two features will aid the differentiation between the IR and SR formulations.

Second, the company propose working with National Poisons Information Centre to ensure dissemination of the revised guidelines for paracetamol treatment and to ensure that doctors are aware that an SR formulation of paracetamol is available.

Although in the uncomplicated case of paracetamol poisoning, the treatment guidelines are simple to apply, clinical judgment is required in many cases e.g. there is uncertainty over the time of ingestion, the concomitant ingestion of other medicines or in cases of staggered overdoses. An overdose of SR paracetamol does not significantly add to the clinical burden of treating paracetamol overdoses, particularly bearing in mind there are clear-cut guidelines on treatment. The maxim applied in the case of IR paracetamol overdose, *if in doubt, treat,* applies as much in cases of SR paracetamol overdoses.

Even if a case were to be mistreated as described above, any risks would appear to be very small. As discussed above, the delayed absorption of paracetamol with the SR formulation may reduce the potential hepatotoxicity due to a slower rate of NAPQI formation.

Although theoretical, clinical data from patients who have taken paracetamol overdose in combination with agents which slow gastro-intestinal motility suggest delayed absorption may reduce the risk of hepatotoxicity.

10. Conclusions

The company has provided data that PANADOL EXTEND fulfils the criteria for a product that can be made available to consumers as a Pharmacy-only Medicine.

The product does not represent a direct or indirect danger when used correctly if utilised without healthcare professional supervision. Paracetamol has an excellent safety profile with a very low incidence of serious adverse events. The safety profiles of PANADOL EXTEND and Panadol Tablets were similar in the four clinical studies. PANADOL EXTEND will be as well tolerated as IR paracetamol.

There are no clinically significant interactions with other commonly used medications and there are no toxicological data that would preclude non-prescription use

The risk of masking a significant underlying condition is extremely small and patients should be able to make an accurate self-assessment of their condition.

The risks associated with incorrect use are likely to be small and certainly no greater that those associated with IR paracetamol. In particular, there is no reason to believe that there is a greater risk of liver toxicity associated with overdosage of PANADOL EXTEND compared to standard IR formulations of paracetamol. Revised treatment guidelines to take account of the possibility of delayed absorption of paracetamol will be developed in conjunction with the appropriate bodies. The risk of inappropriate treatment of overdoses with PANADOL EXTEND is extremely small. The distinctive carton and blister pack will aid differentiation between the standard (IR) and SR formulations and healthcare professionals will be made aware of the new formulation and revised treatment guidelines.

The product is not likely to be used incorrectly to any great extent and if taken at the IR paracetamol dose of 4 times a day there would be no clinical consequences. Similarly the risk of prolonged use of PANADOL EXTEND is extremely small. The risk of abuse or misuse is low.

The company believe that wide accessibility under the supervision of a pharmacist is a benefit and the risks discussed are extremely small.

In conclusion, based on the above, the company consider that this product is suitable for sale as a pharmacy-only medicine and request the MCC recommend the proposed reclassification to allow this to occur.

11. References

1. Dollery CT. (Ed). Therapeutic Drugs. Vol. 1: A19-A21. Edinburgh, Churchill Livingstone, 1999

2. Prescott LF. Paracetamol (acetaminophen). A critical bibliographic review. 1996; Taylor & Francis, London.Ch 15 Adverse Reactions and Interactions pp 353-397.

3. Shek KLA, Chan L-N, Nutescu E. Warfarin-acetaminophen drug interaction revisited. *Pharmacotherapy* 1999: **19**: 1153-1158

4. Prescott LF. Paracetamol overdosage: pharmacological considerations and clinical management. *Drugs* 1983; **25**: 290-314.

5. Mitchell JR, Thorgeirsson SS, Potter WZ, Jollow DJ, Keiser H. Acetaminophen-induced hepatic injury: protective role of glutathione in man and rationale for therapy. *Clin Pharm Ther* 1974; **16**: 676-684.

6. Prescott LF. Paracetamol overdosage: pharmacological considerations and clinical management. *Drugs* 1983; **25**: 290-314

7. Prescott LF. Paracetamol (acetaminophen). A critical bibliographic review. 1996; Taylor & Francis, London.Ch 16 Paracetamol Overdose. pp401-473

8. Paracetamol Information Centre. Guidelines for the Management of Acute Paracetamol Overdosage.

9. McNeil Consumer Healthcare. Guidelines for Management of Acute Acetaminophen Overdose.

10. Burkhart KK. The Acetaminophen nomogram: will it withstand the test of extended relief formulation? Acad Emerg. Med. 1996; **3**: 738-739

11. Pond SM, Tong TG, Kaysen *et al.* Massive intoxication with acetaminophen and propoxyphene: unexpected survival and unusual pharmacokinetics of acetaminophen. J. Toxicol. Clin. Toxicol. 1982; **19**: 1-16.

12. Ruane BJ, Glover G, Varma MPS. Survival after an overdose of Distagesic (dextropropoxyphene and paracetamol). Ulster Med. J. 1989; **58**: 187-189.

13. Block R, Jankowski JAZ, Lacoux P, Pennington CR. Does hypothermia protect against the development of hepatitis in paracetamol overdose? Anaesthesia 1992; **47**: 789-791

14. Vassallo S, Khan Anga, Howland MA. Use of Rumack-Mathew nomogram in cases of extended-release acetaminophen toxicity. Ann. Intern. Med. 1996; **125**: 940

15. Graudins A, Aaron CK, Linden CH. Overdose of extended-release acetaminophen. N.E.J.M. 1995; **333:196**

16. Bizovi KE, Aks SE, Paloucek F, Gross R, Keys N, Rivas J. Late increase in acetaminophen concentration after overdose of Tylenol Extended Relief. Ann. Emerg. Med. 1996; **28**: 549-551

17. Cetaruk EW, Dart RC, Hurlbut KM, Horowitz RS, Shih R. Tylenol Extended Relief overdose. Ann. Emerg. Med. 1997; **30**: 104-108

18. Tighe TV, Walter FG. Delayed toxic acetaminophen level after initial four hour non-toxic level. Clin. Toxicol. 1982; **19**: 1-16

12. Attachments

12.1 Attachment 1: The Expert Report on the Clinical Documentation (UK CER).
12.2 Attachment 2: Correspondence from Medsafe Evaluation Team.
12.3 Attachment 3: Draft Label Copy for PANADOL EXTEND Carton and Blister.
12.4 Attachment 4: Label Comparison of PANADOL EXTEND and regular PANADOL.
12.5 Attachment 5: Personal Communication from Dr Richard Dart regarding Poisons Information Centre experience with extended release formulation in the USA.