SUBMISSION FOR RECLASSIFICATION

OF

SODIUM PICOSULPHATE

(PICOPREP Powder)

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PART A

1. International Non-proprietary Name

Sodium picosulphate

2. Proprietary Name

Picoprep powder (marketed in New Zealand by Pharmatel Pty Ltd)

3. Name of the Company requesting Reclassification

Baxter Healthcare Ltd
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This submission is made by Baxter as the New Zealand distributor *of Fleet Phospho Soda* Buffered Saline Mixture bowel cleansing preparation. In this submission Baxter will show that sodium picosulphate products have a similar safety profile to sodium phosphate products such as *Fleet Phospho-Soda*, and as such should be classified in the same way.

4. Dose Forms and Strengths for which a Change is Sought

Powder for reconstitution.

Containing: 10mg sodium picosulphate, 3.5g magnesium oxide, 12.0g citric acid anhydrous, 36mg aspartame per sachet. Each sachet is reconstituted to 250mL.

5. Pack size and Other Qualifications

Picoprep powder is supplied in packs of 2 sachets.

Reclassification is sought for any strength and pack size of sodium picosulphate.

6. Indications for which Change is Sought

The indications for *Picoprep* powder are:-

Laxative: bowel evacuant prior to gastrointestinal examinations (colonoscopy, bariam enema, X-ray procedures, intravenous pyelograms, surgery or constipation.

NB: These indications are essentially the same as those for *Fleet Phospho Soda* (see data sheet – Attachment 2), although the reasons for bowel evacuation are broader and constipation is included. The indication for constipation has previously been approved for *Fleet Phospho Soda* but was withdrawn by Baxter in order to have a Pharmacist-Only classification for this product.

7. Present Classification of the Medicine

Medicines containing sodium picosulphate are currently classified as Pharmacy Medcines. Thus, *Picoprep* powder is a Pharmacy Medicine.

8. Classification Sought

The proposed classification for medicines containing sodium picosulphate is:-

Sodium picosulphate:	
Except where specified in the First Schedule to the Medicines Regulations 1984	General Sale Medicine

Sodium picosulphate:
In oral preparations for bowel cleansing prior to diagnostic, medical or surgical procedures — Restricted Medicine

Sodium picosulphate:
In oral laxative preparations — Prescription Medicine

NB; These proposed classifications are identical to that currently in place for sodium phosphate preparations.

9. Classification Status in Other Countries

Australia: Until recently sodium picosulphate preparations were unclassified in Australia, making preparations containing this medicine General Sales Medicines. However, a submission was made to the NDPSC to classify these products and considered at its February 2002 meeting. As a result, a new entry for Sodium Picosulphate has been made to Schedule 3 of the SUSDP (see Attachment 1).

Thus, sodium picosulphate in preparations for oral use for bowel cleansing prior to diagnostic, medical or surgical procedures are now classified as Pharmacist Only Medicines (or Restricted Medicines) in Australia.

10. Extent of Usage in New Zealand and Elsewhere

In 2001 approximately 9,150 packs of *Picoprep* were sold in New Zealand.

In 2000, approximately 66,000 packs of *Picoprep* and 51,000 packs of Picolax were sold.

Clearly, these products are more extensively used in Australia than in New Zealand. However, there is some thought that the reason for this higher usage in Australia is due to the products being promoted as ‘safe’ products compared to the alternative sodium phosphate and polyethylene glycol products (polyethylene glycol is also classified as a Pharmacist Only Medicines in Australia for bowel cleansing), and until recently the less restrictive classification of these products supported this view. See Section B for further discussion on this point.

11. Labelling for the Proposed New Presentation

As Baxter does not market any sodium picosulphate presentations, this data cannot be supplied.

12. Proposed Warning Statements

In the next section, Baxter will demonstrate that sodium picosulphate has essentially the same medicinal profile as sodium phosphate presentations, and as such should have similar warning statements (see *Fleet Phospho Soda* Buffered Saline Mixture data sheet – Attachment 2).

13. Other Products Containing the Same Active Ingredient

To the best of Baxter's knowledge, *Picoprep* powder is the only product that contains the active ingredient sodium picosulphate currently in the New Zealand market.

PART B

Reasons for Requesting the Classification Change

Baxter's reasons for requesting this classification change to products containing sodium picosulphate are as follows:-

- the current classification implies that sodium picosulphate is a safer product that sodium phosphate, whereas Baxter believes this is not the case.
- the approved indications are unlikely to be diagnosed by the consumer, and as such a classification that directs the consumer to interaction with a health professional is appropriate
- the product has potential for abuse

A. The Safety of Sodium Picosulphate Preparations

A1. Current Product Information in New Zealand

The current product information available for *Picoprep* powder available in New Zealand (New Ethicals Catalogue May-Nov 2001) is:-

> "**Contraindications:** GI obstruction, gastric retention, bowel performation (frank or suspected), toxic colitis, toxic megacolon and ileus.
> **Precautions:** Severe ulcerative colitis, impaired renal function, pre-existing electrolyte disturbances, those with a stoma, elderly (dehydration and electrolyte depletion may occur), impaired gag reflex, unconscious or semi-concious patients, phenylketonuria."

These contraindications and precautions are very similar to those listed for *Fleet Phospho Soda*. Experience with these types of side effects in New Zealand and elsewhere led to sodium phosphate for bowel cleansing and constipation being more restritively classified, and as such it appears appropriate that sodium picosulphate should also be more restrictively classified that its present classification of Pharmacy Medicine.

Additionally, considering the serious nature of these contraindications and precautions, it is of concern that no data sheet is available for *Picoprep* powder although with the current classification of sodium picosulphate this is not required.

The current adverse effects listed for *Picoprep* in New Zealand are:

> "**Adverse Effects:** Bloating; distension; abdominal pain; nausea. Occasionally, vomiting, anal irritation."

This adverse effect profile does not mention at all the concerns of ADRAC regarding oral sodium picosulphate products (see Section A2 below) and electrlolyte disturbances and their sometimes severe consequences. Such an omission suggests these products need to be more closely regulated than is currently the case.

A2. Experience with Sodium Picosulphate in Australia

In a recent Bulletin (Australian Adverse Drug Reactions Bulletin Vol.21, No.1, February 2002, p2), ADRAC reports as follows:-

> "Low volume bowel preparations for colonoscopy have become increasingly popular in recent years because of the greater comfort for patients who are not required to swallow large volumes of liquid. ADRAC has previously highlighted the risk of severe electrolyte disturbances in association with the use of oral sodium phosphate solution (*Fleet Phospho Soda* Buffered Saline Mixture, Kwikprep) as a bowel preparation. Since then ADRAC has received reports in association with two other products (Picolax, *Picoprep*) which contain sodium picosulphate. Sodium picosulphate acts similarly to sodium phosphate in that it produces its cathartic effect by osmotic action in the gut. This results in a transfer of fluid and electrolytes across the gut to the gut lumen.
>
> **ADRAC has received 16 reports implicating sodium picosulphate products.** * Five described convulsions associated with hyponatraemia.
>
> Another described syncope in a patient with both hyponatraemia and hypokalaemia. There have also been single reports of unconsciousness with hyponatraemia, metabolic alkalosis with hypokalaemia, and 4 of syncope and dehydration without documented electrolyte abnormalities.

> Low volume sodium phosphate and sodium picosulphate products can cause marked dehydration, hyponatraemia, other electrolyte abnormalities and associated complications. Infants, the elderly, the frail and those with congestive heart failure or compromised renal function are particularly at risk. Alternatively less concentrated bowel cleansing preparations should be used in these patients."

(* emphasis added)

Attachment 3 is ADRAC's printout of adverse reports for the range of bowel cleansers on the Australian market. These data show that for the years 2000 and 2001 combined:

- there have been six reports concerning *Picolax* and another four concerning *Picoprep*; and none for the PEG products;
- two reports are recorded for *Fleet Phospho Soda* and another five *for Phosphate-Sandoz*, and one for *Phosphoprep*.

None of the reports involved the death of a patient. However, Baxter and C B Fleet (Aust) Pty Ltd consider that a fair reading of the reports would suggest that the more serious reactions arose in connection with use of the sodium picosulphate preparations. Certainly, this view is supported by the ADRAC report quoted above.

It is clear from these reports that in Australia there have been more recent adverse reports on sodium picosulphate preparations than in respect of sodium phosphate or PEG. Additionally, the figures show that adverse reactions of the kind and severity, and in the numbers, seen in the past for sodium phosphate preparations are no longer being recorded.

In particular, it is of note that there have been no reports of deaths associated with *Fleet Phospho Soda* since the product was scheduled as a Pharmacist Only Medicine in Australia in May 1999, and this fact tends to vindicate the correctness of the NDPSC's decision at the time.

Attachment 4 reproduces material produced by the distributors of sodium picosulphate products in Australia. This material variously claims that:

- *Phosphoprep* induces "significant electrolyte changes", while *Picoprep* brings about "only slight electrolyte change". This is contrary to the view of ADRAC quoted above.
- The *Picoprep* products are "safe", even though the Product Information lists indications, contraindications and precautions similar to those recommended for *Fleet Phospho Soda.*
- *Picoprep* is described as "a gentle laxative or purgative" and for the treatment of "constipation". This indication is not premitted for *Fleet Phospho Soda* in Australia and requires an S4 schedule (Prescription Medicine) for PEG in Australia.

However, it is unknown if this same promotional material is being used in New Zealand for *Picoprep*.

A3. Experience with Sodium Picosulphate in New Zealand

CARM reports that no adverse reactions have been reported for sodium picosulphate products in New Zealand. However, given the relatively limited use of *Picoprep* in New Zealand compared to the sodium picosulphate products in Australia, this result is unsurprising and the much greater Australian experience with the product is probably a better indicator of the overall safety of the product.

B. Ease of Diagnosis by the Consumer

The current indications for *Picoprep* are (New Ethicals Catalogue May-Nov 2001):-

> "Laxative: Bowel evacuant prior to gastrointestinal examinations (colonoscopy, barium enema, x-ray procedures, intravenous pyelograms, surgery) or constipation."

Only the indication for constipation could be considered as suitable for diagnosis by the general public, and gentler and safer laxatives are available for consumers when they consider treatment for constipation is required. Given the

existing contraindications and precautions for sodium picosulphate medicines, and their relatively harsh action compared to other classes of laxatives, a Prescription Medicine classification is appropriate for the constipation indication (as is currently the case for sodium phosphate preparations).

However, as was the case when the classification of sodium phosphate preparations were being considered in New Zealand, it is noted that the typical scenario for usage of this product for bowel evacuation is that when a gastrointestinal examination is considered necessary the patient is contacted by the nurse and instructed regarding the necessity for bowel evacuation. Typically at this point the patient is not in contact with the physician in order to receive a prescription. As such, in order to preserve the current practice, but add additional contact with a health professional regarding the usage of these products, Pharmacist Only Medicine appears to be the best classification for sodium picosulphate medicines for bowel cleansing.

C. Potential for Abuse

Laxative abuse is a well-known phenomena in Western societies. It is believed that those people susceptible to laxative abuse will tend towards harsher and more “cleansing” laxatives, and so it is these laxatives that should be subject to the most restrictive medicine classifications.

Given this consideration, and the current classification of sodium phosphate preparations as Prescription Medicines for oral laxatives, the same classification is considered appropriate for oral sodium picosulphate preparations for laxative use.

In summary, given the details and considerations above, Baxter submits to the Medicines Classification Committee that sodium picosulphate should be treated the same as sodium phosphate for scheduling purposes. Furthermore, Baxter contends that the appropriate level of scheduling to promote patients’ safety and protection should be Restricted Medicine for bowel evacuation and Prescription Medicine for constipation (the current scheduling for sodium phosphate) as this level has proved effective in the case of *Fleet Phospho Soda* (in Australia the incidence and severity of adverse reactions has been greatly reduced for *Fleet Phospho Soda*).