NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Aminophylline Injection
250 mg/10 mL
Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sterile solution of aminophylline (theophylline and ethylenediamine). Each mL contains 25 mg of aminophylline (equivalent to 20.63 mg of theophylline).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DBL Aminophylline Injection 250 mg in 10 mL is a clear, colourless, solution for injection.

The pH of the solution is between 8.8 and 10.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL Aminophylline Injection is indicated for the treatment of reversible bronchospasm associated with chronic bronchitis, emphysema, bronchial asthma and chronic obstructive pulmonary disease. It may also be used for paroxysmal dyspnoea associated with left heart failure.

4.2 Dose and method of administration

DBL Aminophylline Injection may be administered by intravenous infusion, or by slow intravenous injection at a rate not exceeding 20 to 25 mg/min.

Recommended doses are given as a guide only. Dosage must be individualised based on patient characteristics, clinical response, and steady state theophylline concentration. Doses should be calculated on lean (ideal) body weight. Oral theophylline therapy should be substituted for intravenous therapy as soon as adequate improvement has been made.

A loading dose is generally administered over 20 to 30 minutes, followed by a maintenance dose.

Adults and children 6 months and over:

For patients not currently undergoing aminophylline or theophylline therapy, a dose of 6 mg aminophylline/kg lean body weight should be infused over 20 to 30 minutes, to provide a peak
serum theophylline concentration of approximately 10 microgram/mL (55 micromole/L).

For patients currently undergoing aminophylline or theophylline therapy, a serum theophylline concentration should be obtained. The dose of aminophylline may be administered on the principle that 0.6 mg aminophylline/kg lean body weight will increase the serum theophylline concentration by 1 microgram/mL. If it is not possible to obtain serum theophylline concentration, a dose of 3 mg aminophylline/kg lean body weight may be administered.

Table 1 – Loading dose and maintenance dose of Aminophylline based on patient’s age or characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg aminophylline/kg</td>
<td>mg aminophylline/kg/hour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for next 12 h</td>
</tr>
<tr>
<td>Children 6 months to 9 yrs</td>
<td>6 (4.74)*</td>
<td>1.2 (0.95)*</td>
</tr>
<tr>
<td>Children 9 to 16 yrs</td>
<td>6 (4.74)*</td>
<td>1.0 (0.79)*</td>
</tr>
<tr>
<td>Young adult smokers</td>
<td>6 (4.74)*</td>
<td>1.0 (0.79)*</td>
</tr>
<tr>
<td>Non-smoking adults</td>
<td>6 (4.74)*</td>
<td>0.7 (0.55)*</td>
</tr>
<tr>
<td>Older patients or those with cor pulmonae</td>
<td>6 (4.74)*</td>
<td>0.6 (0.47)*</td>
</tr>
<tr>
<td>Patients with congestive heart failure or hepatic failure</td>
<td>6 (4.74)*</td>
<td>0.5 (0.4)*</td>
</tr>
</tbody>
</table>

* Figures in brackets are the equivalent doses of anhydrous theophylline

4.3 Contraindications

DBL Aminophylline Injection is contraindicated in patients hypersensitive to xanthines or to ethylenediamine.

DBL Aminophylline Injection is also contraindicated in patients with coronary artery disease where myocardial stimulation might prove harmful.

DBL Aminophylline Injection is also contraindicated in patients with bronchiolitis (bronchopneumonia).

4.4 Special warnings and precautions for use

General:

Careful consideration of the various interacting drugs and physiologic conditions that can alter theophylline clearance and required dosage adjustment should occur prior to initiation of theophylline therapy and prior to increases in theophylline dose.
Monitoring Serum Theophylline Concentrations:

Serum theophylline concentration measurements are readily available and should be used to determine whether the dosage is appropriate. Specifically, the serum theophylline concentration should be measured as follows:

1. Before making a dose increase to determine whether the serum concentration is sub-therapeutic in a patient who continues to be symptomatic.

2. Whenever signs or symptoms of theophylline toxicity are present.

3. Whenever there is a new illness, worsening of an existing concurrent illness or a change in the patient’s treatment regimen that may alter theophylline clearance (e.g., fever >38.9°C sustained for ≥24 hours, hepatitis, or drugs listed in Table 2 are added or discontinued).

In patients who have received no theophylline in the previous 24 hours, a serum concentration should be measured 30 minutes after completion of the intravenous loading dose to determine whether the serum concentration is <10 mcg/mL indicating the need for an additional loading dose or ≥20 mcg/mL indicating the need to delay starting the constant intravenous infusion. Once the infusion is begun, a second measurement should be obtained after one expected half-life (e.g., approximately 4 hours in children 1 to 9 years and 8 hours in non-smoking adults; see Table 4 for the expected half-life in additional patient populations). The second measurement should be compared to the first to determine the direction in which the serum concentration has changed. The infusion rate can then be adjusted before steady state is reached in an attempt to prevent an excessive or sub-therapeutic theophylline concentration from being achieved.

If a patient has received theophylline in the previous 24 hours, the serum concentration should be measured before administering an intravenous loading dose to make sure that it is safe to do so. If a loading dose is not indicated (i.e., the serum theophylline concentration is ≥10 mcg/mL), a second measurement should be obtained as above at the appropriate time after starting the intravenous infusion. If, on the other hand, a loading dose is indicated (see section 4.2 Dose and method of administration for guidance on selection of the appropriate loading dose), a second blood sample should be obtained after the loading dose and a third sample should be obtained one expected half-life after starting the constant infusion to determine the direction in which the serum concentration has changed.

Once the above procedures related to initiation of intravenous theophylline infusion have been completed, subsequent serum samples for determination of theophylline concentration should be obtained at 24-hour intervals for the duration of the infusion. The theophylline infusion rate should be increased or decreased as appropriate based on the serum theophylline levels.

When signs or symptoms of theophylline toxicity are present, the intravenous infusion should be stopped and a serum sample for theophylline concentration should be obtained as soon as possible, analyzed immediately, and the result reported to the clinician without delay. In patients in whom decreased serum protein binding is suspected (e.g., cirrhosis, women during the third trimester of pregnancy), the concentration of unbound theophylline should be measured and the dosage adjusted to achieve an unbound concentration of 6-12 mcg/mL.
Saliva concentrations of theophylline cannot be used reliably to adjust dosage without special techniques.

**Conditions That Reduce Theophylline Clearance:**

DBL Aminophylline Injection should be used with extreme caution in patients currently undergoing therapy with other xanthines, such as theophylline, as the hazard of serious toxicity is increased.

There are several readily identifiable causes of reduced theophylline clearance. *If the infusion rate is not appropriately reduced in the presence of these risk factors, severe and potentially fatal theophylline toxicity can occur.* Careful consideration must be given to the benefits and risks of theophylline use and more intensive monitoring of serum theophylline concentrations should always be obtained in these patients prior to any aminophylline administration.

Since clearance may be decreased and hence toxicity may be more likely in these patients, DBL Aminophylline Injection should be used with caution in patients with the following risk factors:

1) **Age**
   - Neonates (term and premature)
   - Children <1 year
   - Elderly (>60 years)

2) **Concurrent Diseases**
   - Congestive heart failure
   - Chronic alcoholism
   - Acute febrile illness (>38.9°C for 24 hours or more) or lesser temperature elevations for longer periods
   - Chronic obstructive pulmonary disease
   - Cor pulmonale
   - Influenza or those undergoing influenza immunization
   - Renal dysfunction including reduced renal function in infants <3 months of age
   - Hepatic dysfunction, including hepatic cirrhosis, acute hepatitis
   - Hypothyroidism
   - Acute pulmonary oedema or pneumonia
   - Sepsis with multi-organ failure
   - Shock

3) **Smoking cessation**

DBL Aminophylline Injection may lower the seizure threshold and should be administered with caution in patients with seizure disorder unless the patient is receiving appropriate anticonvulsant therapy. Dose adjustment of any anticonvulsant medication may be required.

DBL Aminophylline Injection should be administered with caution in patients with the following clinical conditions due to the increased risk of exacerbation of the concurrent condition:

- Active peptic ulcer
- Seizure disorders
- Hyperthyroidism
- Hypertension
- Glaucoma
- Diabetes mellitus
- Cardiac arrhythmias (excluding bradyarrhythmias)
- Gastroesophageal reflux

Where myocardial stimulation would be harmful, DBL Aminophylline Injection should be administered with caution in patients with:

- Compromised cardiac or circulatory function
- Angina pectoris
- Acute myocardial injury

Intravenous aminophylline must be administered slowly and cautiously to prevent dangerous CNS or cardiovascular toxicity. Too rapid intravenous administration may result in the following symptoms: anxiety, headache, nausea and vomiting, severe hypotension, dizziness, faintness, lightheadedness, palpitations, syncope, precordial pain, flushing, profound bradycardia, premature ventricular contractions, cardiac arrest.

Intramuscular administration is not recommended as it causes intense local pain and sloughing of tissue.

The coagulation time of the blood is shortened with aminophylline therapy.

**When Signs or Symptoms of Theophylline Toxicity Are Present:**
Whenever a patient receiving theophylline develops nausea or vomiting, particularly repetitive vomiting, or other signs or symptoms consistent with theophylline toxicity (even if another cause may be suspected), the intravenous infusion should be stopped and a serum theophylline concentration measured immediately.

**Dosage Increases**
Increases in the dose of intravenous theophylline should not be made in response to an acute exacerbation of symptoms unless the steady-state serum theophylline concentration is <10 mcg/mL.

As the rate of theophylline clearance may be dose-dependent (i.e., steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a sub-therapeutic serum concentration measurement should be conservative. In general, limiting infusion rate increases to about 25% of the previous infusion rate will reduce the risk of unintended excessive increases in serum theophylline concentration.

**Use in the elderly**

DBL Aminophylline Injection should be administered with caution. Elderly patients are at significantly greater risk of experiencing serious toxicity from theophylline than younger patients due to pharmacokinetic and pharmacodynamic changes associated with aging. Theophylline clearance is reduced in patients greater than 60 years of age, resulting in increased
serum theophylline concentrations in response to a given theophylline infusion rate. Protein binding may be decreased in the elderly resulting in a larger proportion of the total serum theophylline concentration in the pharmacologically active unbound form. Elderly patients also appear to be more sensitive to the toxic effects of theophylline after chronic overdosage than younger patients. For these reasons, the maximum infusion rate of theophylline in patients greater than 60 years of age ordinarily should not exceed 17 mg/hr (21 mg/hr as aminophylline) unless the patient continues to be symptomatic and the peak steady state serum theophylline concentration is <10 mcg/mL.

Theophylline infusion rates greater than 17 mg/hr (21 mg/hr as aminophylline) should be prescribed with caution in elderly patients.

**Paediatric use**

DBL Aminophylline Injection should be administered with caution in premature or neonatal infants and children <1 year.

The constant infusion rate of intravenous theophylline must be selected with caution in pediatric patients since the rate of theophylline clearance is highly variable across the age range of neonates to adolescents.

Due to the immaturity of theophylline metabolic pathways in pediatric patients under the age of one year, particular attention to dosage selection and frequent monitoring of serum theophylline concentrations are required when theophylline is prescribed to pediatric patients in this age group.

Children are particularly sensitive to xanthines, especially the CNS stimulant effects. The margin of safety above therapeutic doses is small. Rapid intravenous injection is not recommended in children.

**Effects on laboratory tests**

As a result of its pharmacological effects, theophylline at serum concentrations within the 10 - 20 mcg/mL range modestly increases plasma glucose (from a mean of 88 mg/dL to 98 mg/dL), uric acid (from a mean of 4 mg/dL to 6 mg/dL), free fatty acids (from a mean of 451 µEq/L to 800 µEq/L), total cholesterol (from a mean of 140 vs 160 mg/dL), HDL (from a mean of 36 to 50 mg/dL), HDL/LDL ratio (from a mean of 0.5 to 0.7), and urinary free cortisol excretion (from a mean of 44 to 63 mcg/24 hr). Theophylline at serum concentrations within the 10 - 20 mcg/mL range may also transiently decrease serum concentrations of triiodothyronine (144 before, 131 after one week and 142 ng/dL after 4 weeks of theophylline). The clinical importance of these changes should be weighed against the potential therapeutic benefit of theophylline in individual patients.

The Effect of Other Drugs on Theophylline Serum Concentration Measurements:

Most serum theophylline assays in clinical use are immunoassays which are specific for theophylline. Other xanthines such as caffeine, dyphylline, and pentoxifylline are not detected by these assays. Some drugs (e.g., cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in neonates or patients with renal
dysfunction may cause the reading from some dry reagent office methods to be higher than the actual serum theophylline concentration.

Dipyridamole-assisted myocardial perfusion studies:

Aminophylline reverses the effects of dipyridamole on myocardial blood flow, thereby interfering with the test results. Dipyridamole-assisted myocardial perfusion studies should not be performed if therapy with aminophylline cannot be withheld for 36 hours prior to the test.

Uric acid serum determinations:

Aminophylline produces false-positive elevations of serum uric acid as measured by the Bittner or colorimetric methods, but not by the uricase method.

4.5 Interaction with other medicines and other forms of interaction

The following drugs may inhibit theophylline metabolism and decrease aminophylline clearance resulting in increased serum levels and the potential for increased toxicity: alcohol, high dose allopurinol (> 600 mg/day), beta-blockers, cimetidine, oestrogen containing oral contraceptives, diltiazem, disulfiram, recombinant alpha-interferon, methotrexate, mexiletine, propranolol, tacrine, thiabendazole, thyroid hormones, ticlopidine, verapamil, and macrolide antibiotics and quinolones (including erythromycin, clarithromycin, ciprofloxacin and enoxacin).

The following drugs may enhance theophylline metabolism and increase the clearance of aminophylline, and thereby decrease serum concentrations, possibly resulting in subtherapeutic dosing: aminoglutethimide barbiturates including phenobarbitone and primidone, carbamazepine, isoprenaline, phenytoin, rifampicin, St John’s wort (Hypericum perforatum), sulfinpyrazone, thioamines and tobacco and marijuana smoking.

In addition, the following drugs may interact with aminophylline:

Adenosine
Aminophylline may antagonise the cardiovascular effects of adenosine.

Beta-agonists
Concurrent use of aminophylline and beta-agonists may produce increased cardiotoxic effects. Also, aminophylline may potentiating the hypoglycaemia which may be associated with administration of beta-agonists.

Beta-blocking agents (including ophthalmic agents)
Concurrent use of aminophylline and beta-blockers may result in an inhibition of the bronchodilatory effects of aminophylline.

Benzodiazepines
Concurrent use of aminophylline and benzodiazepines may result in a reduction or reversal of the sedative effects of benzodiazepines.

Cardiac glycosides
Aminophylline may enhance the sensitivity of the myocardium to, and the toxic potential of cardiac glycosides.

**Ephedrine and other sympathomimetic amines**
Concurrent use of aminophylline and sympathomimetic amines may result in increased nausea, nervousness or insomnia.

**Halothane**
Concurrent use of aminophylline and halothane may result in ventricular arrhythmias.

**Ketamine**
Concurrent use of aminophylline and ketamine may result in a lowered seizure threshold.

**Lithium**
Concurrent use of aminophylline and lithium may result in increased excretion of lithium, and hence a reduction in the therapeutic effect of lithium. Adjustment of the lithium dosage may be required.

**Neuromuscular blocking agents, non-depolarizing**
Aminophylline may antagonize the neuromuscular blocking effects of these agents.

**Xanthines**
Concurrent use of aminophylline and other xanthine containing medications may result in additive toxicity and should be avoided (see section 4.3).

The drugs listed in **Table 2** have the potential to produce clinically significant pharmacodynamic or pharmacokinetic interactions with theophylline. The information in the “Effect” column of **Table 2** assumes that the interacting drug is being added to a steady-state theophylline regimen. If theophylline is being initiated in a patient who is already taking a drug that inhibits theophylline clearance (e.g., cimetidine, erythromycin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be smaller. Conversely, if theophylline is being initiated in a patient who is already taking a drug that enhances theophylline clearance (e.g., rifampicin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be larger. Discontinuation of a concomitant drug that increases theophylline clearance will result in accumulation of theophylline to potentially toxic levels, unless the theophylline dose is appropriately reduced. Discontinuation of a concomitant drug that inhibits theophylline clearance will result in decreased serum theophylline concentrations, unless the theophylline dose is appropriately increased.

The drugs listed in **Table 3** have either been documented not to interact with theophylline or do not produce a clinically significant interaction (i.e., <15% change in theophylline clearance).

New interactions are continuously being reported for theophylline, especially with new chemical entities. **The clinician should not assume that a drug does not interact with theophylline if it is not listed in Table 2.** Before addition of a newly available drug in a patient receiving theophylline, the package insert of the new drug and/or the medical literature should be consulted to determine if an interaction between the new drug and theophylline has been reported.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Type Of Interaction</th>
<th>Effect**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>Theophylline blocks adenosine receptors.</td>
<td>Higher doses of adenosine may be required to achieve desired effect.</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Decreases theophylline clearance at allopurinol doses ≥600 mg/day.</td>
<td>25% increase</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Similar to aminogluthimide.</td>
<td>30% decrease</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Decreases theophylline clearance by inhibiting cytochrome P450 1A2.</td>
<td>70% increase</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Similar to cimetidine.</td>
<td>40% increase</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Similar to erythromycin.</td>
<td>25% increase</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Benzodiazepines increase CNS concentrations of adenosine, a potent CNS depressant, while theophylline blocks adenosine receptors.</td>
<td>Larger diazepam doses may be required to produce desired level of sedation. Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression.</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Decreases theophylline clearance by inhibiting hydroxylation and demethylation.</td>
<td>50% increase</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Synergistic CNS effects.</td>
<td>Increased frequency of nausea, nervousness, and insomnia.</td>
</tr>
<tr>
<td>Ethanol</td>
<td>A single large dose of ethanol (3 mL/kg of whiskey) decreases theophylline clearance for up to 24 hours.</td>
<td>30% increase</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin metabolite decreases theophylline clearance by inhibiting cytochrome P450 3A3.</td>
<td>35% increase. Erythromycin steady-state serum concentrations decrease by a similar amount.</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Similar to diazepam.</td>
<td>Similar to diazepam.</td>
</tr>
</tbody>
</table>
Table 2 - Clinically Significant Drug Interactions With Theophylline* (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type Of Interaction</th>
<th>Effect**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>Similar to cimetidine.</td>
<td>Similar to cimetidine.</td>
</tr>
<tr>
<td>Halothane</td>
<td>Halothane sensitizes the myocardium to catecholamines, theophylline increases release of endogenous catecholamines.</td>
<td>Increased risk of ventricular arrhythmias.</td>
</tr>
<tr>
<td>Interferon, human recombinant alpha-A</td>
<td>Decreases theophylline clearance.</td>
<td>100% increase</td>
</tr>
<tr>
<td>Isoprenaline (I.V.)</td>
<td>Increases theophylline clearance.</td>
<td>20% decrease</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Pharmacologic</td>
<td>May lower theophylline seizure threshold.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Theophylline increases renal lithium clearance.</td>
<td>Lithium dose required to achieve a therapeutic serum concentration increased an average of 60%.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Similar to diazepam.</td>
<td>Similar to diazepam.</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>Decreases theophylline clearance.</td>
<td>20% increase after low dose MTX, higher dose MTX may have a greater effect.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Similar to diazepam.</td>
<td>Similar to diazepam.</td>
</tr>
<tr>
<td>Oestrogen</td>
<td>Oestrogen containing oral contraceptives decrease theophylline clearance in a dose-dependent fashion. The effect of progesterone on theophylline clearance is unknown.</td>
<td>30% increase</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Theophylline may antagonize nondepolarizing neuromuscular blocking effects; possibly due to phosphodiesterase inhibition.</td>
<td>Larger dose of pancuronium may be required to achieve neuromuscular blockade.</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Decreases theophylline clearance.</td>
<td>30% increase</td>
</tr>
<tr>
<td>Phenobarbital (PB)</td>
<td>Similar to aminogluthethimide.</td>
<td>25% decrease after two weeks of concurrent Phenobarbital.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Phenytoin increases theophylline clearance by increasing microsomal enzyme activity. Theophylline decreases phenytoin absorption.</td>
<td>Serum theophylline and phenytoin concentrations decrease about 40%.</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Decreases theophylline clearance and pharmacologic interaction.</td>
<td>40% increase. Beta-2 blocking effect may decrease efficacy of theophylline.</td>
</tr>
</tbody>
</table>
### Table 2 - Clinically Significant Drug Interactions With Theophylline* (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type Of Interaction</th>
<th>Effect**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Similar to cimetidine and pharmacologic interaction.</td>
<td>100% increase. Beta-2 blocking effect may decrease efficacy of theophylline.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Increases theophylline clearance by increasing cytochrome P450 1A2 and 3A3 activity.</td>
<td>20 - 40% decrease</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Decreases theophylline clearance.</td>
<td>60% increase</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Similar to disulfiram.</td>
<td>20% increase</td>
</tr>
</tbody>
</table>

* Refer to text above Table 2 for further information regarding table.

** Average effect on steady-state theophylline concentration or other clinical effect for pharmacologic interactions. Individual patients may experience larger changes in serum theophylline concentration than the value listed.

### Table 3 - Drugs That Have Been Documented Not to Interact With Theophylline or Drugs That Produce No Clinically Significant Interaction With Theophylline*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin</td>
<td>mebendazole</td>
</tr>
<tr>
<td>atenolol</td>
<td>medroxyprogesterone</td>
</tr>
<tr>
<td>azithromycin</td>
<td>methylprednisolone</td>
</tr>
<tr>
<td>caffeine, dietary ingestion</td>
<td>metronidazole</td>
</tr>
<tr>
<td>cefaclor</td>
<td>metoprolol</td>
</tr>
<tr>
<td>co-trimoxazole (trimethoprim and sulfamethoxazole)</td>
<td>nifedipine</td>
</tr>
<tr>
<td>diltiazem</td>
<td>norfloxacin</td>
</tr>
<tr>
<td>famotidine</td>
<td>omeprazole</td>
</tr>
<tr>
<td>felodipine</td>
<td>prednisone, prednisolone</td>
</tr>
<tr>
<td>finasteride</td>
<td>ranitidine</td>
</tr>
<tr>
<td>hydrocortisone</td>
<td>rifabutin</td>
</tr>
<tr>
<td>isoflurane</td>
<td>roxithromycin</td>
</tr>
<tr>
<td>isoniazid</td>
<td>salbutamol, systemic and inhaled</td>
</tr>
<tr>
<td>isradipine</td>
<td>sorbitol</td>
</tr>
<tr>
<td>influenza vaccine</td>
<td>(purgative doses do not inhibit theophylline absorption)</td>
</tr>
<tr>
<td>ketoconazole</td>
<td>sucralfate</td>
</tr>
<tr>
<td></td>
<td>terbutaline, systemic tetracycline</td>
</tr>
</tbody>
</table>

* Refer to text above Table 2 for information regarding table.
4.6 Fertility, pregnancy and lactation

Effects on fertility

In a 14 week continuous breeding study, theophylline, administered to mating pairs of B6C3F1 mice at oral doses of 120, 270 and 500 mg/kg (approximately 1.0 - 3.0 times the human dose on a mg/m² basis) impaired fertility, as evidenced by decreases in the number of live pups per litter, decreases in the mean number of litters per fertile pair, and increases in the gestation period at the high dose as well as decreases in the proportion of pups born alive at the mid and high dose. In 13 week toxicity studies, theophylline was administered to F344 rats and B6C3F1 mice at oral doses of 40 - 300 mg/kg (approximately 2 times the human dose on a mg/m² basis). At the high dose, systemic toxicity was observed in both species including decreases in testicular weight.

Use in pregnancy – Category A

The pharmacokinetics of aminophylline may be altered during pregnancy, and therefore serum theophylline concentrations may need to be measured more frequently in patients undergoing aminophylline therapy during pregnancy.

Use in lactation

Aminophylline, as theophylline, is distributed into breast milk, and may occasionally induce irritability or other signs of toxicity in the breast fed infants of mothers undergoing aminophylline therapy. The concentration of theophylline in breast milk is about equivalent to the maternal serum concentration. An infant ingesting a liter of breast milk containing 10 - 20 mcg/mL of theophylline per day is likely to receive 10 - 20 mg of theophylline per day. Serious adverse effects in the infant are unlikely unless the mother has toxic serum theophylline concentrations.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are <20 mcg/mL and mainly consist of transient caffeine-like adverse effects such as nausea, vomiting, headache, and insomnia. When peak serum theophylline concentrations exceed 20 mcg/mL, however, theophylline produces a wide range of adverse reactions including persistent vomiting, cardiac arrhythmias, and intractable seizures which can be lethal.

Other adverse reactions that have been reported at serum theophylline concentrations <20 mcg/mL include diarrhea, irritability, restlessness, fine skeletal muscle tremors, and transient diuresis. In patients with hypoxia secondary to COPD, multifocal atrial tachycardia

\[^{1}\text{Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.}\]
and flutter have been reported at serum theophylline concentrations ≥15 mcg/mL. There have been a few isolated reports of seizures at serum theophylline concentrations <20 mcg/mL in patients with an underlying neurological disease or in elderly patients. The occurrence of seizures in elderly patients with serum theophylline concentrations <20 mcg/mL may be secondary to decreased protein binding resulting in a larger proportion of the total serum theophylline concentration in the pharmacologically active unbound form. The clinical characteristics of the seizures reported in patients with serum theophylline concentrations <20 mcg/mL have generally been milder than seizures associated with excessive serum theophylline concentrations resulting from an overdose (i.e., they have generally been transient, often stopped without anticonvulsant therapy, and did not result in neurological residua).

Products containing aminophylline may rarely produce severe allergic reactions of the skin, including exfoliative dermatitis, after systemic administration in a patient who has been previously sensitized by topical application of a substance containing ethylenediamine. In such patients skin patch tests are positive for ethylenediamine, a component of aminophylline, and negative for theophylline. Pharmacists and other individuals who experience repeated skin exposure while physically handling aminophylline may develop a contact dermatitis due to the ethylenediamine component.

**Cardiovascular system:** Tachycardia, palpitations, extrasystoles, increased pulse rate, flushing, hypotension, circulatory failure, atrial and ventricular arrhythmia, peripheral vasoconstriction.

**Central nervous system:** Headache, nervousness, insomnia, irritability, restlessness, dizziness, reflex hyperexcitability, seizures, anxiety, tremor, lightheadedness, excitement.

**Gastrointestinal system:** Nausea, vomiting, heartburn, epigastric pain, abdominal cramps, anorexia, diarrhoea, haematemesis.

**Genitourinary:** Increased urination, albuminuria.

**Other:** Fever.

**Respiratory system:** Tachypnoea.

**Skin and appendages:** Ethylenediamine hypersensitivity induced dermatitis (hives, skin rash, sloughing of skin).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions [https://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/).

**4.9 Overdose**

The chronicity and pattern of theophylline overdosage significantly influences clinical manifestations of toxicity, management and outcome. There are two common presentations: 1) acute overdose, i.e., infusion of an excessive loading dose or excessive maintenance infusion
rate for less than 24 hours, and 2) chronic overdosage, i.e., excessive maintenance infusion rate for greater than 24 hours.

The most common causes of chronic theophylline overdosage include clinician prescribing of an excessive dose or a normal dose in the presence of factors known to decrease the rate of theophylline clearance and increasing the dose in response to an exacerbation of symptoms without first measuring the serum theophylline concentration to determine whether a dose increase is safe.

Clinical features

Less severe toxicities do not always precede major toxicities. Chronic overdose may produce toxicity at serum levels lower than those in acute overdose. Potentially life threatening toxicities may occur at serum concentration greater than 40 microgram/mL (220 micromole/L) in chronic overdose. In acute overdose serum concentrations greater than 90 microgram/mL (495 micromole/L) are generally associated with severe toxicity.

The following signs and symptoms may be present in aminophylline overdose:

- **cardiovascular**: tachycardia, arrhythmias, palpitations, hypotension.
- **central nervous system**: agitation, confusion or altered behaviour including toxic psychosis, seizures.
- **gastrointestinal**: nausea, vomiting, diarrhoea and/or hematemesis, continuing or severe abdominal pain, acute pancreatitis.
- **genitourinary**: renal failure.
- **metabolic**: hyperglycaemia, hypokalaemia, metabolic acidosis, hypophosphataemia, hypercalcaemia.
- **respiratory**: tachypnea, respiratory arrest, respiratory alkalosis.
- **other**: extreme thirst, slight fever, tinnitus.

In general, patients who experience an acute overdose are less likely to experience seizures than patients who have experienced a chronic overdosage, unless the peak serum theophylline concentration is >100 mcg/mL. After a chronic overdosage, generalized seizures, life-threatening cardiac arrhythmias, and death may occur at serum theophylline concentrations >30 mcg/mL. The severity of toxicity after chronic overdosage is more strongly correlated with the patient’s age than the peak serum theophylline concentration; patients >60 years are at the greatest risk for severe toxicity and mortality after a chronic overdosage. Pre-existing or concurrent disease may also significantly increase the susceptibility of a patient to a particular toxic manifestation, e.g., patients with neurologic disorders have an increased risk of seizures and patients with cardiac disease have an increased risk of cardiac arrhythmias for a given serum theophylline concentration compared to patients without the underlying disease.

Other manifestations of theophylline toxicity include increases in serum calcium, creatine kinase, myoglobin and leukocyte count, decreases in serum phosphate and magnesium, acute myocardial infarction, and urinary retention in men with obstructive uropathy. Seizures
associated with serum theophylline concentrations >30 mcg/mL are often resistant to anticonvulsant therapy and may result in irreversible brain injury if not rapidly controlled. Death from theophylline toxicity is most often secondary to cardiorespiratory arrest and/or hypoxic encephalopathy following prolonged generalized seizures or intractable cardiac arrhythmias causing hemodynamic compromise.

**Treatment**

There is no specific antidote for aminophylline overdose. Treatment of overdose is symptomatic and supportive. Administration of sympathomimetic drugs should be avoided. Treatment may involve the following measures:

- Administration of oral activated charcoal, regardless of the route of exposure to aminophylline (this assists in decreasing the serum concentration of theophylline by interrupting the enterohepatic circulation). Oral activated charcoal should be repeated until the serum theophylline concentration is below 20 microgram/mL.

- Charcoal hemoperfusion to increase the elimination of aminophylline. Hemodialysis is less effective in eliminating aminophylline, but may be warranted in some patients.

- Administration of intravenous diazepam to control seizures. Where diazepam is ineffective, phenytoin, phenobarbitone, or thiopentone may be considered.

- Correction of fluid and electrolyte balance.

- Support of respiratory functions by airway management, oxygen administration or mechanical ventilation as required.

- Support of cardiac functions. Propranolol may be warranted in the presence of extreme tachycardia, and antiarrythmic therapy may be required.

- Administration of phenothiazines in the presence of life threatening hypothermia.

- Monitoring of serum theophylline concentrations and ECG.

**General Recommendations for Patients with Symptoms of Theophylline Overdose or Serum Theophylline Concentrations >30 mcg/mL While Receiving Intravenous Theophylline as Aminophylline.**

1. Stop the aminophylline (theophylline) infusion.

2. While simultaneously instituting treatment, contact a regional poison center to obtain updated information and advice on individualizing the recommendations that follow.

3. Institute supportive care, including establishment of intravenous access, maintenance of the airway, and electrocardiographic monitoring.

4. **Treatment of seizures:** Because of the high morbidity and mortality associated with theophylline-induced seizures, treatment should be rapid and aggressive. Anticonvulsant therapy should be initiated with an intravenous benzodiazepine, e.g., diazepam, in increments of 0.1 - 0.2 mg/kg every 1 - 3 minutes until seizures are terminated. Repetitive seizures should be treated with a loading dose of phenobarbital (20 mg/kg infused over 30 - 60 minutes). Case reports of theophylline overdose in humans and animal studies suggest that phenytoin is ineffective in terminating theophylline-induced seizures. The doses of benzodiazepines and phenobarbital...
required to terminate theophylline-induced seizures are close to the doses that may cause severe respiratory depression or respiratory arrest; the clinician should therefore be prepared to provide assisted ventilation. Elderly patients and patients with COPD may be more susceptible to the respiratory depressant effects of anticonvulsants. Barbiturate-induced coma or administration of general anesthesia may be required to terminate repetitive seizures or status epilepticus. General anesthesia should be used with caution in patients with theophylline overdose because fluorinated volatile anesthetics may sensitize the myocardium to endogenous catecholamines released by theophylline. Enflurane appears less likely to be associated with this effect than halothane and may, therefore, be safer. Neuromuscular blocking agents alone should not be used to terminate seizures since they abolish the musculoskeletal manifestations without terminating seizure activity in the brain.

5. **Anticipate Need for Anticonvulsants:** In patients with theophylline overdose who are at high risk for theophylline-induced seizures, e.g., patients with acute overdoses and serum theophylline concentrations >100 mcg/mL or chronic overdosage in patients >60 years of age with serum theophylline concentrations >30 mcg/mL, the need for anticonvulsant therapy should be anticipated. A benzodiazepine such as diazepam should be drawn into a syringe and kept at the patient’s bedside and medical personnel qualified to treat seizures should be immediately available. In selected patients at high risk for theophylline-induced seizures, consideration should be given to the administration of prophylactic anticonvulsant therapy. Situations where prophylactic anticonvulsant therapy should be considered in high risk patients include anticipated delays in instituting methods for extracorporeal removal of theophylline (e.g., transfer of a high risk patient from one health care facility to another for extracorporeal removal) and clinical circumstances that significantly interfere with efforts to enhance theophylline clearance (e.g., a neonate where dialysis may not be technically feasible or a patient with vomiting unresponsive to antiemetics who is unable to tolerate multiple-dose oral activated charcoal). In animal studies, prophylactic administration of phenobarbital, but not phenytoin, has been shown to delay the onset of theophylline-induced generalized seizures and to increase the dose of theophylline required to induce seizures (i.e., markedly increases the LD$_{50}$). Although there are no controlled studies in humans, a loading dose of intravenous phenobarbital (20 mg/kg infused over 60 minutes) may delay or prevent life-threatening seizures in high risk patients while efforts to enhance theophylline clearance are continued. Phenobarbital may cause respiratory depression, particularly in elderly patients and patients with COPD.

6. **Treatment of cardiac arrhythmias:** Sinus tachycardia and simple ventricular premature beats are not harbingers of life-threatening arrhythmias, they do not require treatment in the absence of hemodynamic compromise, and they resolve with declining serum theophylline concentrations. Other arrhythmias, especially those associated with hemodynamic compromise, should be treated with antiarrhythmic therapy appropriate for the type of arrhythmia.

7. **Serum Theophylline Concentration Monitoring:** The serum theophylline concentration should be measured immediately upon presentation, 2 - 4 hours later, and then at sufficient intervals, e.g., every 4 hours, to guide treatment decisions and to assess the effectiveness of therapy. Serum theophylline concentrations may continue to increase after presentation of the patient for medical care as a result of continued absorption of theophylline from the gastrointestinal tract. Serial monitoring of serum theophylline serum concentrations should be continued until it is clear that the concentration is no longer rising and has returned to nontoxic levels.
8. **General Monitoring Procedures:** Electrocardiographic monitoring should be initiated on presentation and continued until the serum theophylline level has returned to a nontoxic level. Serum electrolytes and glucose should be measured on presentation and at appropriate intervals indicated by clinical circumstances. Fluid and electrolyte abnormalities should be promptly corrected. **Monitoring and treatment should be continued until the serum concentration decreases below 20 mcg/mL.**

9. **Enhance clearance of theophylline:** Multiple-dose oral activated charcoal (e.g., 0.5 mg/kg up to 20 g, every two hours) increases the clearance of theophylline at least twofold by adsorption of theophylline secreted into gastrointestinal fluids. Charcoal must be retained in, and pass through, the gastrointestinal tract to be effective; emesis should therefore be controlled by administration of appropriate antiemetics. Alternatively, the charcoal can be administered continuously through a nasogastric tube in conjunction with appropriate antiemetics. A single dose of sorbitol may be administered with the activated charcoal to promote stooling to facilitate clearance of the adsorbed theophylline from the gastrointestinal tract. Sorbitol alone does not enhance clearance of theophylline and should be dosed with caution to prevent excessive stooling which can result in severe fluid and electrolyte imbalances. Commercially available fixed combinations of liquid charcoal and sorbitol should be avoided in young children and after the first dose in adolescents and adults since they do not allow for individualization of charcoal and sorbitol dosing. In patients with intractable vomiting, extracorporeal methods of theophylline removal should be instituted (see section 4.9 Overdose, Extracorporeal Removal).

**Specific Recommendations:**

**Acute Overdose (e.g., excessive loading dose or excessive infusion rate <24 hours)**

A. **Serum Concentration >20 <30 mcg/mL**
   1. Stop the theophylline infusion.
   2. Monitor the patient and obtain a serum theophylline concentration in 2 - 4 hours to insure that the concentration is decreasing.

B. **Serum Concentration >30 <100 mcg/mL**
   1. Stop the theophylline infusion.
   2. Administer multiple dose oral activated charcoal and measures to control emesis.
   3. Monitor the patient and obtain serial theophylline concentrations every 2 - 4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.
   4. Institute extracorporeal removal if emesis, seizures, or cardiac arrhythmias cannot be adequately controlled (see section 4.9 Overdose, Extracorporeal Removal).

C. **Serum Concentration >100 mcg/mL**
   1. Stop the theophylline infusion.
   2. Consider prophylactic anticonvulsant therapy.
   3. Administer multiple-dose oral activated charcoal and measures to control emesis.
   4. Consider extracorporeal removal, even if the patient has not experienced a seizure (see section 4.9 Overdose, Extracorporeal Removal).
   5. Monitor the patient and obtain serial theophylline concentrations every 2 - 4 hours to gauge the effectiveness of therapy and to guide further treatment decisions.

**Chronic Overdosage (e.g., excessive infusion rate for greater than 24 hours)**

A. **Serum Concentration >20 <30 mcg/mL (with manifestations of theophylline toxicity)**
   1. Stop the theophylline infusion.
   2. Monitor the patient and obtain a serum theophylline concentration in 2 - 4 hours to insure that the concentration is decreasing.
B. Serum Concentration >30 mcg/mL in patients <60 years of age
   1. Stop the theophylline infusion.
   2. Administer multiple-dose oral activated charcoal and measures to control emesis.
   3. Monitor the patient and obtain serial theophylline concentrations every 2 - 4 hours to
gauge the effectiveness of therapy and to guide further treatment decisions.
   4. Institute extracorporeal removal if emesis, seizures, or cardiac arrhythmias cannot be
   adequately controlled (see section 4.9 Overdose, Extracorporeal Removal).

C. Serum Concentration >30 mcg/mL in patients ≥60 years of age
   1. Stop the theophylline infusion.
   2. Consider prophylactic anticonvulsant therapy.
   3. Administer multiple-dose oral activated charcoal and measures to control emesis.
   4. Consider extracorporeal removal even if the patient has not experienced a seizure (see
   section 4.9 Overdose, Extracorporeal Removal).
   5. Monitor the patient and obtain serial theophylline concentrations every 2 - 4 hours to
gauge the effectiveness of therapy and to guide further treatment decisions.

Extracorporeal Removal:
Increasing the rate of theophylline clearance by extracorporeal methods may rapidly decrease
serum concentrations, but the risks of the procedure must be weighed against the potential
benefit. Charcoal hemoperfusion is the most effective method of extracorporeal removal,
increasing theophylline clearance up to six fold, but serious complications, including
hypotension, hypocalcemia, platelet consumption and bleeding diatheses may occur.
Hemodialysis is about as efficient as multiple-dose oral activated charcoal and has a lower risk
of serious complications than charcoal hemoperfusion. Hemodialysis should be considered as
an alternative when charcoal hemoperfusion is not feasible and multiple-dose oral charcoal is
ineffective because of intractable emesis. Serum theophylline concentrations may rebound
5 - 10 mcg/mL after discontinuation of charcoal hemoperfusion or hemodialysis due to
redistribution of theophylline from the tissue compartment. Peritoneal dialysis is ineffective
for theophylline removal; exchange transfusions in neonates have been minimally effective.

For advice on the management of overdose please contact the National Poisons Centre on 0800
POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
Aminophylline is a 2:1 complex of theophylline and ethylenediamine. Aminophylline has
greater water solubility than theophylline. In biological fluids aminophylline dissociates to
theophylline hence the pharmacological effects of aminophylline are those of theophylline.
Theophylline is a xanthine derivative with the main pharmacological action of direct relaxation
of bronchial smooth muscle, relieving bronchospasm. The bronchodilatory effect of
theophylline is minimal if bronchospasm is not the cause. The bronchodilatory effect may be
via inhibition of selected phosphodiesterases, which produces an increase in intracellular
cyclic AMP. Theophylline also directly stimulates the medullary respiratory centre. Other
pharmacological effects of theophylline include stimulation of cardiac muscle (increasing both
heart rate and myocardial contractility at higher doses), stimulation of the central nervous
system, transient diuresis, increased gastric secretion, decreased peripheral resistance and cerebral vasoconstriction.

5.2 Pharmacokinetic properties

Absorption

Aminophylline dissociates rapidly to theophylline in biological fluids.

Distribution

Theophylline is rapidly distributed throughout non-adipose tissues and extracellular fluids. Theophylline crosses the placenta, and is distributed into breast milk. The concentration of theophylline in breast milk is approximately 70% that found in the serum. The apparent volume of distribution of theophylline is 0.3 to 0.7 L/kg (average 0.45 L/kg).

Approximately 60% of theophylline in adults and 35% in premature infants and neonates is bound to plasma proteins.

Metabolism

Theophylline undergoes hepatic metabolism via the cytochrome P450 system. In adults the main metabolites are 1,3-dimethyl uric acid, 1-methyl uric acid, and 3-methylxanthine.

Excretion

Theophylline and its metabolites undergo renal excretion.

There is significant interpatient variability in the pharmacokinetics of theophylline, and hence aminophylline. The serum half life of theophylline in otherwise healthy, non-smoking, asthmatic adults averages 7 to 9 hours, and theophylline clearance in this group is reported to be approximately 0.65 mL/kg/hr. Serum half life is increased and clearance decreased in the elderly and in patients with congestive heart failure, chronic obstructive pulmonary disease, cor pulmonale or liver disease. Serum half life is decreased and clearance increased in cigarette or marijuana smokers. Clearance in premature infants and neonates is reduced. Theophylline clearance increases during the first year of life and remains relatively constant during the first 9 years, then gradually declines to adult values by 16 years of age.

Theophylline, (and hence aminophylline), has a low therapeutic index. Serum theophylline concentrations of around 5 to 20 microgram/mL (27.5 to 110 micromole/L) are generally considered therapeutic. Serum theophylline concentrations greater than 20 microgram/mL (110 micromoles/L) are often associated with adverse reactions.

5.3 Preclinical safety data

Genotoxicity

Theophylline has been studied in Ames salmonella, in vivo and in vitro cytogenetics, micronucleus and Chinese hamster ovary test systems and has not been shown to be genotoxic.
Carcinogenicity
No data available.

Reproductive and developmental toxicity
No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water for injections

6.2 Incompatibilities
Aminophylline precipitates in acidic media, but this does not apply to the dilute solutions in intravenous infusion fluids.

Aminophylline containing solutions are alkaline, and hence drugs known to be alkali labile should not be added to aminophylline containing solutions.

Aminophylline injection should not be mixed in a syringe with other drugs but should be added separately to the intravenous solution. When an intravenous solution containing aminophylline is given “piggyback”, the intravenous system already in place should be turned off while the aminophylline is infused if there is a potential problem with admixture incompatibility.

Aminophylline is reported to be incompatible with the following drugs:

Adrenaline, amiodarone, ascorbic acid, benzylpenicillin, chlorpromazine hydrochloride, ciprofloxacin, clindamycin, codeine phosphate, diltiazem, dimenhydrinate, dobutamine, doxapram, erythromycin gluceptate, hydralazine, hydroxyzine HCl, insulin, isoprenaline HCl, methadone HCl, methicillin sodium, morphine sulfate, noradrenaline acid tartrate, oxytetracycline hydrochloride, penicillin G potassium, pentazocine lactate, pethidine HCl, phenobarbitone sodium, phenytoin sodium, potassium, prochlorperazine edisylate, promazine hydrochloride, promethazine hydrochloride, ondansetron, tetracycline hydrochloride, vancomycin hydrochloride, vitamin B complex with C.

6.3 Shelf life
30 months.

6.4 Special precautions for storage
Store below 25°C. Protect from light.
6.5 Nature and contents of container

<table>
<thead>
<tr>
<th>Strength</th>
<th>Pack size</th>
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<tr>
<td>250 mg in 10 mL</td>
<td>5 x 10 mL ampoules, glass</td>
</tr>
<tr>
<td>250 mg in 10 mL</td>
<td>50 x 10 mL ampoules, glass</td>
</tr>
</tbody>
</table>

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

09 July 1981

10. DATE OF REVISION OF THE TEXT

6 April 2022

Summary table of changes

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<td>1.</td>
<td>Removal of BP claim from Product nomenclature</td>
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