New Zealand Data Sheet

1. PRODUCT NAME
   Penthrox® 1.5mL volatile liquid for inhalation
   Penthrox® 3mL volatile liquid for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Penthrox® 1.5mL bottle contains 1.5mL of Methoxyflurane 99.9% w/w
   Penthrox® 3mL bottle contains 3mL of Methoxyflurane 99.9% w/w
   For full list of excipients see, section 6.1

3. PHARMACEUTICAL FORM
   Volatile liquid for inhalation
   Clear, almost colourless mobile liquid, with a characteristic odour (mildly pungent odour)

4. CLINICAL PARTICULARS
   4.1. Therapeutic indications
       - For emergency relief of pain by self-administration in conscious haemodynamically stable patients with trauma and associated pain, under supervision of personnel trained in its use (see section 4.2)
       - For the relief of pain in monitored conscious patients who require analgesia for surgical procedures such as the change of dressings (see section 4.2)

   4.2. Dose and method of administration
       Penthrox® (methoxyflurane) is self-administered under observation (and assisted if necessary) by a person trained in its administration using the hand held Penthrox® Inhaler. The cumulative dose received by patients receiving intermittent doses of Penthrox® (methoxyflurane) for painful procedures (such as wound dressings) must be carefully monitored to ensure that the recommended dose of methoxyflurane is not exceeded.

       Adults:
       One bottle of Penthrox® (1.5 mL or 3 mL) to be vaporised in a Penthrox® inhaler. On finishing the initial bottle, another bottle may be used. Up to 6 mL may be administered per day; the total maximum dose must not be exceeded.

       Patient should be instructed to inhale intermittently to achieve adequate analgesia. Continuous administration will reduce time of analgesia. To maximise safety, the
lowest effective dosage of Penthrox® (methoxyflurane) to provide analgesia should be used. Administration of consecutive days or daily use is not recommended because of nephrotoxic potential and the total weekly dose should not exceed 15 mL. Exceeding the recommended dose may cause renal failure, see section 4.4.

Children:
Limited data is available regarding the administration of Penthrox® using the Penthrox® Inhaler; see section 4.4- Special warnings and precautions for use. The minimum effective dose to produce analgesia should be administered to children.

Elderly:
The minimum effective dose to produce analgesia should be administered see section 4.4- Special warnings and precautions for use

Method of Administration
Instructions on the preparation of the Penthrox® Inhaler and correct administration are provided in Figure 1.

Figure 1: How to use the Penthrox® Inhaler

1. Ensure the Activated Carbon (AC) Chamber (where applicable) is inserted into the dilutor hole on the top of the Penthrox® Inhaler.

2. Holding the Penthrox® bottle upright, use the base the Penthrox® Inhaler to loosen the cap with a ½ turn. Separate the Inhaler from the bottle and remove the cap by hand.

3. Tilt the Penthrox® Inhaler to a 45° angle and pour the contents of one bottle into the base whilst rotating.
Place wrist loop over patient’s wrist. Patient inhales through the mouthpiece of Inhaler to obtain analgesia. First few breaths should be gentle and then breathe normally through Inhaler.

Patient exhales into Inhaler. The exhaled vapour passes through the AC Chamber to adsorb any exhaled Penthrox®.

If stronger analgesia is required, patient can cover dilutor hole with finger during inhalation.

Patient should be instructed to inhale intermittently to achieve adequate analgesia. Continuous administration will reduce time of analgesia. Patients should be administered minimum dose.

### 4.3. Contraindications

- Use as an anaesthetic agent
- Renal impairment, including reduced glomerular filtration rate (GFR), urine output and reduced renal blood flow.
- Renal failure
- Hypersensitivity to fluorinated anaesthetics or any ingredients in Penthrox®
- Cardiovascular instability
- Respiratory depression
- Head injury or loss of consciousness
- A history of possible adverse reactions in either patient or relatives
- Malignant hyperthermia: patients with known or genetically susceptible to malignant hyperthermia
4.4. Special warnings and precautions for use

Renal disease
Penthrox® impairs renal function in a dose-related manner due to the effect of the released fluoride on the distal tubule and may cause polyuric or oliguric renal failure, oxaluria being the prominent feature. Nephrotoxicity is greater with Penthrox® than with other halogenated anaesthetics because of the slower metabolism over several days resulting in prolonged production of fluoride ions and metabolism to other potentially nephrotoxic substances. Methoxyflurane-associated renal failure is generally irreversible. Because of the potential nephrotoxic effects Penthrox® must not be used as an anaesthetic agent. Furthermore, the lowest effective dose of Penthrox® should be administered, especially in aged or obese patients see section 5.2.

Liver disease
It is advisable not to administer Penthrox® to patients who have shown signs of liver damage, especially after previous Penthrox® or halothane anaesthesia. There have also been occasional reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis, see section 4.8.

Paediatric population
Paediatric neurotoxicity:
Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans. Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia
should take into consideration the benefits of the procedure weighed against the potential risks (see also section 4.6).

**Diabetic patients:**
May have an increased likelihood of developing nephropathy if they have impaired renal function or polyuria, are obese, or are not optimally controlled.

**Cardiovascular effects / Use in elderly**
Caution should be exercised in the elderly due to possible reduction in blood pressure or heart rate.

**Occupational exposure**
Health workers who are regularly exposed to patients using Penthrox® inhalers should be aware of any relevant occupational health and safety guidelines for the use of inhalational agents. The use of methods to reduce occupational exposure to Penthrox®, including the attachment of the Penthrox® Activated Carbon (AC) Chamber, should be considered. Multiple use creates additional risk. Elevation of liver enzymes, blood urea nitrogen and serum uric acid have been reported in exposed maternity ward staff.

### 4.5. Interaction with other medicines and other forms of interaction

**Enzyme inducing drugs:**
In patients under treatment with enzyme inducing drugs (e.g. barbiturates) the metabolism of Penthrox® may be enhanced resulting in increased risk of nephrotoxicity.

**Adrenaline or noradrenaline:**
Intravenous adrenaline or nor-adrenaline should be employed cautiously during Penthrox® administration.

**Drugs with nephrotoxic effects:**
The concurrent use of tetracycline and Penthrox® for anaesthesia has been reported to result in fatal renal toxicity. The possibility exists that Penthrox® may enhance the adverse renal effects of other drugs including certain antibiotics of known nephrotoxic potential such as gentamicin, kanamycin, colistin, polymyxin B, cephaloridine and amphotericin B.

**Narcotics:**
If given concomitantly with Pethrox, the patient should be observed closely, and the dosage for the subsequent administration of narcotics may be reduced.
6-blockers:
Interaction may occur with β-blockers, with an increased risk of hypotension.

4.6. Fertility, pregnancy and lactation

Pregnancy
Risk summary statement:
Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Preclinical data
Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

Other information
All general anaesthetics’ cross the placenta and carry the potential to produce central nervous system and respiratory depression in the new born infant. In routine practice this dose does not appear to be a problem; however in a compromised foetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

Neonates delivered of mothers who used Penthrox® analgesia for childbirth had a briefly raised serum uric acid, not requiring further intervention.

Preeclampsia/Toxaemia of pregnancy
It is advisable not to administer Penthrox® due to the possibility of existing renal impairment.

Breast-feeding
Caution should be exercised when Penthrox® is administered to a nursing mother.

4.7. Effects ability to drive and use machines
The decision as to when patients may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be
individualised. Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate a machine until the patient has completely recovered from the effects of the drug, such as drowsiness. The treating doctor should decide when activities such as driving a vehicle or operating a machine may be resumed.

4.8. Undesirable effects
There are no data on the dose-dependency of most of the adverse drug reactions.

Use of Penthrox® in patients with trauma and associated pain:
The following Table provides treatment-emergent adverse events experienced; using System Organ Class and Preferred Term; by ≥1% of the safety population of a placebo-controlled study in patients with trauma and associated pain, of which 149 had Penthrox®.

<table>
<thead>
<tr>
<th></th>
<th>Methoxyflurane in Inhaler (N=149)</th>
<th>Placebo In Inhaler (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>N (%)</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>188</td>
<td>88 (59.1%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>13</td>
<td>12 (8.1%)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>3</td>
<td>3 (2.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>2</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>General Disorders And Administration Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditions</td>
<td>10</td>
<td>9 (6.0%)</td>
</tr>
<tr>
<td>Influenza Like Illness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>2</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Infections And Infestations</td>
<td>8</td>
<td>7 (4.7%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>2</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>2</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Category</td>
<td>Total</td>
<td>Percent</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Injury, Poisoning And Procedural Complications</strong></td>
<td>9</td>
<td>4.0%</td>
</tr>
<tr>
<td>Fall</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Joint sprain</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>8</td>
<td>3.4%</td>
</tr>
<tr>
<td>Alanine Aminotransferase increased</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Aspartate Aminotransferase increased</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Blood lactate dehydrogenase increased</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td><strong>Musculoskeletal And Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>3</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>118</td>
<td>49.7%</td>
</tr>
<tr>
<td>Amnesia</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>50</td>
<td>29.5%</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>51</td>
<td>21.5%</td>
</tr>
<tr>
<td>Migraine</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8</td>
<td>5.4%</td>
</tr>
<tr>
<td><strong>Reproductive System and Breast disorders</strong></td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic And Mediastinal Disorders</strong></td>
<td>5</td>
<td>3.4%</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>1.3%</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>3</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>Skin And Subcutaneous Tissue Disorders</strong></td>
<td>5</td>
<td>3.4%</td>
</tr>
</tbody>
</table>
n=number of events, N=number of patients, %=percentage of patients.

In listings below, are Adverse Reactions (adverse effects that are related to the treatment) which occurred at a rate lower than in the Table above. They are listed by system organ class and frequency (common ≥1/100 to <1/10: uncommon ≥1/1,000 to <1/100; and rare ≥1/10,000 to <1/1,000).

Nervous system disorders: Uncommon: Dysgeusia, Paraesthesia
Gastrointestinal disorders: Uncommon: Oral discomfort
General disorders and administration site conditions: Uncommon: Fatigue, Feeling abnormal, Feeling of relaxation, Hangover, Hunger, Shivering
Eye disorders: Uncommon: Diplopia
Psychiatric disorders: Uncommon: Inappropriate affect

Use of Penthrox® for pain relief in patients who require it for surgical procedures: The following Table provides drug-associated events (Adverse Reactions) experienced by ≥ 2% of the safety population of a placebo-controlled study in patients in a minor surgical procedure, of which 49 had Penthrox® for the relief of pain.

<table>
<thead>
<tr>
<th></th>
<th>Methoxyflurane In Inhaler (N=49)</th>
<th>Placebo In Inhaler (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Adverse events 30-45 mins after Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (8.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>2 (4.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1 (2%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (2%)</td>
<td>1 (2.1%)</td>
</tr>
</tbody>
</table>
Post-marketing experience:
The following additional adverse effects have also been reported in the literature in association with analgesia:

Nervous system disorders: drowsiness, sleepy, agitation, restlessness, dissociation
Respiratory system: choking
Hepatic: hepatitis
Renal: increased serum uric acid, urea nitrogen and creatinine
Eyes: blurred vision, nystagmus
Hepatic toxicity in association with methoxyflurane is rare but has been observed with analgesic use.

The following adverse effects have been reported in association with historical use as an anaesthetic:

Common: retrograde amnesia, nausea, vomiting, coughing, drowsiness, sleeping, dizziness, dislike of odour, fever, polyuria, headache.

<table>
<thead>
<tr>
<th></th>
<th>1 (2%)</th>
<th>0 (0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neuropathy: sensory</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Somnolence / depressed level of consciousness</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0%)</td>
<td>1 (2.1%)</td>
</tr>
</tbody>
</table>

**Adverse events 48 Hours after Procedure**

<table>
<thead>
<tr>
<th></th>
<th>2 (4.1%)</th>
<th>0 (0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence / depressed level of consciousness</td>
<td>2 (4.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Confusion</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Musculoskeletal / soft tissue</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Rare: non-specific hepatitis, malignant hyperthermia
Other reported events: cardiac arrest, respiratory depression, laryngospasm, bronchospasm, hypotension, bradycardia, renal failure, increased serum urea, increased serum creatinine, increased urinary oxalate excretion, increased serum inorganic fluoride, pallor, muscle relaxation

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 reactions
https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Symptoms Patients should be observed for signs of drowsiness, pallor and muscle relaxation following Penthrox® administration. High doses of Penthrox® cause dose related nephrotoxicity.

Treatment In the event of excessive urinary output following overdosage, fluid and electrolyte losses should be promptly replaced.

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

Pharmacotherapeutic Group: Other analgesics
ATC code N02BG09

Mechanism of action
Penthrox® vapour provides analgesia when inhaled at low concentrations. After Penthrox® administration, drowsiness may occur. During Penthrox® administration, the cardiac rhythm is usually regular. The myocardium is only minimally sensitised to adrenaline by Penthrox®. In Plane 1- Light anaesthesia, some decrease in blood pressure may occur. This may be accompanied by bradycardia. The hypotension noted is accompanied by reduced cardiac contractile force and reduced cardiac output.

5.2. Pharmacokinetic properties

Absorption:
Partition coefficients at 37 °C
A water/gas coefficient of 4.5
A Blood/gas coefficient (mean range) of 10.20 to 14.06
An Oil/gas coefficient of 825
The vapour concentration of Penthrox® is limited by its vapour pressure at room temperature to a maximum of about 3.5% at 23°C

Distribution:
Penthrox® has great propensity to diffuse into fatty tissues. Hence Penthrox® is released slowly from this reservoir and becomes available for biotransformation for many days.

Metabolism:
Biotransformation of Penthrox® occurs in man. As much as 50-70% of the absorbed dose is metabolised to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. Both the free fluoride and the oxalic acid can cause renal damage in large doses, however dose-related nephrotoxicity seen with clinical doses appears related to a combination of free fluoride and dichloroacetic acid. Penthrox® is more susceptible to metabolism than other halogenated methyl ethyl ethers

Elimination:
Approximately 20% of Penthrox® uptake is recovered in the exhaled air, while urinary excretion of organic fluorine, fluoride and oxalic acid accounts for about 30% of the Penthrox® uptake. Studies have shown that higher peak blood fluoride levels are obtained earlier in obese than in non-obese and in the elderly.

5.3. Preclinical safety data
Animal toxicology and/or pharmacology
Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal
apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Butylated hydroxytoluene

6.2. Incompatibilities
Not applicable

6.3. Shelf life
36 months from date of manufacture

6.4. Special precautions for storage
Store below 30°C

6.5. Nature and contents of container
Penthrox® (methoxyflurane) is supplied in the following presentations:
  a) 3 mL sealed bottle with a tear off tamper seal (pack of 10),
  b) Combination pack with one 3 mL sealed bottle and one Penthrox® Inhaler (pack of 1 or 10) with or without optional Activated Carbon (AC) Chamber,
  c) Combination pack with two 3 mL sealed bottles and one Penthrox® Inhaler (pack of 10), and
  d) Combination pack with one 1.5 mL sealed bottle and one Penthrox® Inhaler (pack of 1 or 10) with AC Chamber.

6.6. Special precautions for disposal and other handling
The refilling must be conducted in a well-ventilated area to reduce environmental exposure to Penthrox® vapour.

7. MEDICINE SCHEDULE
Prescription Medicine.
8. SPONSOR
Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL
04 April 2002

10. DATE OF REVISION OF THE TEXT
04 May 2017

Summary table of changes

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4</td>
<td>Special warnings and precaution for use – new section added: Paediatric population</td>
</tr>
<tr>
<td>4.6</td>
<td>Fertility, pregnancy and lactation – new section added: Pregnancy risk summary statement and Preclinical data</td>
</tr>
<tr>
<td>5.1</td>
<td>Pharmacotherapeutic Group and ATC code added</td>
</tr>
<tr>
<td>5.3</td>
<td>Preclinical safety data – new section added: Animal toxicology and/or pharmacology</td>
</tr>
</tbody>
</table>