1 NAME OF THE MEDICINE
Moxonidine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Physiotens tablets are immediate release film-coated tablets for oral use containing 0.2 mg or 0.4 mg moxonidine.
Excipients with known effect: Lactose monohydrate
For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM
Moxonidine is a white to almost white powder with a melting point of 197 – 205°C.
Physiotens 0.2 mg tablets: Pale pink, round, biconvex, film-coated tablet, imprinted 0.2 on one side.
Physiotens 0.3 mg tablets: Pink, round, biconvex, film coated tablet, imprinted with 0.3 on one side.
Physiotens 0.4 mg tablets: Brick-red, round, biconvex, film-coated tablet, imprinted 0.4 on one side.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Physiotens is indicated for the treatment of hypertension.

4.2 DOSE AND METHOD OF ADMINISTRATION
Treatment should be started with 0.2 mg Physiotens in the morning. The dose may be titrated after two weeks to 0.4 mg given as one dose or as divided doses (morning and evening) until a satisfactory response is achieved. If the response is still unsatisfactory after a further 2 weeks treatment, the dosage can be increased up to a maximum of 0.6 mg in divided doses (morning and evening).
A single daily dose of 0.4 mg and a divided daily dose of 0.6 mg of Physiotens should not be exceeded.
Physiotens may be taken with or without food.

4.3 CONTRAINDICATIONS
Hypersensitivity to any of the ingredients (see Section 6.1 List of excipients).
Heart failure (NYHA Class I – IV).
Patients aged 75 years or older (see Section 5.2 Pharmacokinetic properties - Pharmacokinetics in the elderly).
Bradycardia (HR < 50 beats/minute) or severe bradyarrhythmia, including sick sinus syndrome, or second or third degree atrioventricular (AV) block.
Malignant arrhythmias.
Severe renal impairment (GFR < 30 mL/min, serum creatinine concentration >160 μmol/L).
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cessation of combination therapy with beta-blockers
Abrupt cessation of combination therapy with moxonidine and a beta-blocker may result in rebound hypertension. If combination therapy with moxonidine and a beta-blocker is to be ceased, the beta-blocker should be stopped first and then moxonidine stopped after a few days have elapsed. During cessation of therapy blood pressure should be regularly monitored.

Atrioventricular block
Cases of varying degrees of AV block have been reported in the post-marketing setting in patients undergoing moxonidine treatment. Based on these case reports, the causative role of moxonidine in delaying atrioventricular conduction cannot be completely ruled out. Therefore, caution is recommended when treating patients with a possible predisposition to developing an AV block.

When moxonidine is used in patients with 1st degree AV block, special care should be exercised to avoid bradycardia. Moxonidine must not be used in higher degree AV blocks (see Section 4.3 Contraindications).

Other
Physiotens should be used with caution in patients with a history of angioneurotic oedema.

As with other centrally acting antihypertensives, moxonidine should be used with caution in patients with severe coronary artery disease and unstable angina. There is limited experience in this population.

Moxonidine should not be used because of lack of experience in cases of intermittent claudication, Raynaud’s Disease, Parkinson’s Disease, epileptic disorders, glaucoma, and depression.

Due to lack of therapeutic experience, the use of moxonidine concomitantly with alcohol or tricyclic antidepressants should be avoided.

In limited studies, no rebound effect of the blood pressure after sudden discontinuation of moxonidine treatment has been detected. Nevertheless, it is advised not to interrupt the intake of moxonidine abruptly. Moxonidine should be withdrawn gradually over a period of days.

Due to the presence of lactose in Physiotens tablets, patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Use in Renal Impairment
Caution is advised in the administration of moxonidine to patients with renal impairment as moxonidine is excreted primarily via the kidney. In these patients, careful titration of the dose is recommended, especially at the start of therapy. In patients with moderate renal impairment (GFR 30 – 60 mL/min), the single dose should not exceed 0.2 mg and the daily dose should not exceed 0.4 mg of moxonidine. The hypotensive effect of moxonidine should be closely monitored, especially at the start of treatment (see Section 4.2 Dose and method of administration).

Use in the Elderly
See Sections 4.3 Contraindications and 5.2 Pharmacokinetic properties - Pharmacokinetics in the Elderly.

Paediatric Use
Physiotens should not be given to children below the age of 16 years as insufficient therapeutic experience exists in this group.

Effects on Laboratory Tests
In controlled clinical trials, clinically important changes in standard laboratory parameters possibly associated with administration of moxonidine were rarely observed and occurred at rates comparable to those seen with placebo.
4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concurrent administration of other antihypertensive agents enhances the hypotensive effect of moxonidine.

The sedative effect of tricyclic antidepressants, tranquilizers, alcohol, sedatives, hypnotics and benzodiazepines can be potentiated by moxonidine. Moxonidine moderately augmented the impaired performance in cognitive functions in subjects receiving lorazepam.

Since tricyclic antidepressants may reduce the effectiveness of centrally acting antihypertensive agents, it is not recommended that tricyclic antidepressants be co-administered with moxonidine.

In healthy volunteers, no pharmacokinetic interactions have been observed with glibenclamide or digoxin.

4.6 MOXONIDINE IS EXCRETED THROUGH TUBULAR EXCRETION. INTERACTION WITH OTHER AGENTS THAT ARE EXCRETED THROUGH TUBULAR EXCRETION CANNOT BE EXCLUDED. FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
Moxonidine did not affect fertility of rats at oral doses up to 6.4 mg/kg/day (15-64 times the clinical exposure at 0.3 mg BID, based on plasma moxonidine concentration).

Use in Pregnancy
Pregnancy Category: B3

Moxonidine was not teratogenic in rats. It caused abortions, increased embryofoetal losses, and/or delayed foetal development at high oral doses (≥ 9 mg/kg/day in rats and 4.9 mg/kg/day in rabbits), associated with maternal toxicity. No adverse effects on embryofoetal development were seen at 2 mg/kg/day in rats and 0.6 mg/kg/day in rabbits. Exposures at the no effect dose were 24 (rat, based on AUC) and 22 (rabbit, based on dose adjusted for body surface area) times the clinical exposure at the maximum recommended clinical dose (0.3 mg BID).

There is inadequate data in pregnant women or women of childbearing age, and as such moxonidine should not be used during pregnancy unless the benefit clearly justifies the possible risk to the foetus.

Use in Lactation
Oral administration of moxonidine to rats from late pregnancy until weaning was associated with maternotoxicity, reduced pup weight and viability, and delayed pup development at ≥ 3 mg/kg/day, with no effects at 1 mg/kg/day (approximately 12 times the clinical exposure at 0.3 mg BID, based on AUC).

Studies in humans have shown that moxonidine passed from the maternal blood stream to breast milk. As the effect on the newborn infant is unknown, moxonidine should not be used by nursing mothers, unless the benefits clearly justify the possible risks to the infants.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on its pharmacodynamic properties, moxonidine is unlikely to affect the ability to drive or operate machinery. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Moxonidine has been evaluated for safety in over 4000 subjects worldwide, including more than 1200 patients treated for more than 6 months and over 800 patients treated for 1 year or longer. Most adverse events were of mild or moderate severity and did not require discontinuation of therapy.
In placebo-controlled clinical trials, 4.7% of patients treated with moxonidine discontinued therapy due to clinical adverse experiences, compared to 2.5% discontinuations among placebo-treated patients. The table below lists adverse events that occurred at an incidence of 1% or more among moxonidine-treated patients who participated in placebo-controlled trials of 6 to 8 weeks’ duration, using doses of 0.2 mg to 0.8 mg daily.

**Table 1: Treatment Emergent Adverse Events in all Placebo-Controlled Trials with a Frequency ≥ 1% by Body System and all Cardiovascular Adverse Events**

<table>
<thead>
<tr>
<th>Body System</th>
<th>% Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event (Preferred Term)</strong></td>
<td>Moxonidine (n=886)</td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>5.6</td>
</tr>
<tr>
<td>Headache</td>
<td>7.7</td>
</tr>
<tr>
<td>Infection</td>
<td>1.0</td>
</tr>
<tr>
<td>Pain</td>
<td>1.4</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.0</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Metabolic and Nutritional System</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10.4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.0</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td>6.2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1.8</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.4</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Skin and Appendages</strong></td>
<td>2.3</td>
</tr>
<tr>
<td>Rash</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Urogenital System</strong></td>
<td>2.3</td>
</tr>
</tbody>
</table>
Post-marketing Adverse Events
Common (≥1/100 and <1/10): dry mouth, headache, dizziness, nausea, sleep disturbance, somnolence, asthenia, vasodilatation, anxiety.

Uncommon (≥1/1000 and <1/100): sedation, insomnia, skin rash, urticaria, pruritus.

Rare (≥1/10000 and <1/1000): hypotension, postural hypotension.

Very Rare (<1/10000): angioedema.

Reporting Suspected Adverse Effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE
Oral dosages up to 2.0 mg/day have been tolerated without the occurrence of serious adverse events. The following case of accidental overdose with Physiotens by a 2 year old child has been reported: The child ingested an unknown quantity of Physiotens. The maximum dosage possibly ingested was 14 mg. The child had the following symptoms: sedation, coma, hypotension, miosis and dyspnoea. Gastric Lavage, glucose infusion, mechanically assisted ventilation and rest resulted in the complete disappearance of the symptoms in 11 hours.

Because of the pharmacodynamic properties of moxonidine, the following symptoms can be expected in adults: sedation, hypotension, orthostatic dysregulation, bradycardia, dry mouth, somnolescence, headache, dizziness, asthenia, fatigue and upper abdominal pain. In rare cases emesis, tachycardia, hyperglycemia and paradoxical hypertension may occur. No specific treatment is known. Phentolamine (Regitine) may, depending on the dose, reverse part of the symptoms of moxonidine overdose. Measures to support blood circulation are recommended.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action
In different animal models, moxonidine has been shown to be a relatively potent antihypertensive agent. Available experimental data suggest that the site of the antihypertensive action of moxonidine is the central nervous system (CNS). Moxonidine has been shown to bind to I1-imidazoline receptors and to a lesser extent α2-adrenoreceptors. The therapeutic action of moxonidine appears to result from interaction with I1 and α2-receptors located within the rostral ventrolateral medulla, leading to a reduced activity of sympathetic nerves.

Moxonidine differs from other available centrally acting antihypertensives by exhibiting only low affinity to central α2-adrenoceptors compared to I1-imidazoline receptors; α2-adrenoceptors are considered the molecular target via which sedation and dry mouth, the most common side effects of centrally acting antihypertensives, are mediated. In humans, moxonidine leads to a reduction of systemic vascular resistance and consequently in arterial blood pressure.

Clinical Trials
The antihypertensive effects of moxonidine were demonstrated in three placebo- and reference-controlled pivotal trials, studying dosages of 0.2 to 0.6 mg once daily in patients with mild to moderate hypertension (office diastolic blood pressure 95 – 110 mmHg; 24-hour ambulatory diastolic blood pressure ≥ 85 mmHg). The studies allowed direct comparison of moxonidine to a reference agent (enalapril) at equipotent doses, analysis of peak and trough effects, and (in pooled data) an evaluation of the dose response relationship. In all, 464 patients were included,
of whom 152 were randomized to moxonidine. All studies were double-blind, placebo and reference-controlled, prospectively randomized, parallel group comparisons, with a 4-week placebo run-in period followed by 8 weeks double-blind treatment.

The first study compared 0.2 mg moxonidine with 5 mg enalapril and placebo once daily. The intent-to-treat patient population comprised 169 patients evaluable for office blood pressure and 152 for ABPM. The mean placebo-subtracted differences in office systolic/diastolic blood pressure at trough from baseline to week 8 were -3.40/-4.65 mmHg for moxonidine. The reduction for diastolic blood pressure was statistically significant versus placebo (p<0.001) and not different from enalapril. The difference in systolic blood pressure did not differ statistically from placebo. The overall incidence of adverse events of moxonidine (27.8%) was similar to enalapril (26.7%) and placebo (22.8%) in this trial.

In the second study of similar design, 0.4 mg moxonidine was compared with 10 mg enalapril and placebo once daily. A total of 139 patients were included in the intent-to-treat sample for office blood pressure and 108 patients for ABPM. Moxonidine reduced office systolic and diastolic blood pressures at trough highly statistically significantly by 13.08/7.01 mmHg (placebo-corrected; p<0.001 for both) and was equivalent to enalapril. Similar results were obtained with the 24-hour, daytime and night-time ABPM values. The 24-hour effects were maintained over the dosing interval with a trough to peak ratio of approximately 70%. Treatment emergent adverse events were reported in 36.6% of the moxonidine patients, in 31.9% of the enalapril patients and in 28.9% with placebo.

In the third pivotal study of similar design, 0.6 mg moxonidine was compared with 20 mg enalapril and placebo once daily. The intent-to-treat population consisted of 154 patients for office blood pressure measurements and 130 for ABPM. Office systolic and diastolic blood pressures were markedly and statistically significantly reduced by moxonidine by 21.53/10.45 mmHg (placebo-corrected; p < 0.001 for both) in comparison to placebo and did not differ from enalapril. Mean 24-hour ABPM was statistically reduced versus placebo for both diastolic and systolic blood pressures as well. Adverse events were recorded for 43.1% of patients in the moxonidine group in comparison to 32.1% in the enalapril group and 22.6% with placebo.

The main efficacy results for the primary and secondary parameters can be taken from the Table below.

<table>
<thead>
<tr>
<th>Name of Study (Study Number)</th>
<th>K220.5053</th>
<th>K220.5047</th>
<th>S220.3102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>171</td>
<td>139</td>
<td>154</td>
</tr>
<tr>
<td>Dose of moxonidine</td>
<td>0.2 mg OD</td>
<td>0.4 mg OD</td>
<td>0.6 mg OD</td>
</tr>
<tr>
<td>Dose of reference therapy</td>
<td>5 mg enalapril OD</td>
<td>10 mg enalapril OD</td>
<td>20 mg enalapril OD</td>
</tr>
<tr>
<td>Change from baseline in sitting DBP at trough (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxonidine (+/- SD)</td>
<td>-10.7 (7.6)</td>
<td>-12.3 (8.7)</td>
<td>-13.2 (8.4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>-7.0 (9.0)</td>
<td>-4.7 (6.8)</td>
<td>-2.3 (7.0)</td>
</tr>
<tr>
<td>Difference to placebo (95% CI)</td>
<td>-4.65 (-7.3; -2.03)</td>
<td>-7.01 (-4.46; -9.57)</td>
<td>-10.45 (-13.0; -7.91)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reference (enalapril)</td>
<td>-12.3 (7.7)</td>
<td>-11.8 (8.0)</td>
<td>-11.9 (7.5)</td>
</tr>
<tr>
<td>Difference to reference (95% CI)</td>
<td>0.95 (-1.52; 3.42)</td>
<td>-0.37 (-2.90; 2.16)</td>
<td>-1.17 (-3.65; 1.30)</td>
</tr>
<tr>
<td>Change from baseline in sitting SBP at trough (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxonidine (+/- SD)</td>
<td>-12.1 (13.9)</td>
<td>-19.5 (16.0)</td>
<td>-24.9 (20.7)</td>
</tr>
</tbody>
</table>
The combination of hydrochlorothiazide and moxonidine was evaluated in a further placebo-controlled, double-blind and prospectively randomized trial. The study comprised a total of 161 randomized patients: 37 received moxonidine 0.4 mg, 40 received hydrochlorothiazide 25 mg, 42 received the combination 0.4/25 mg and 41 received placebo, all once daily. Sitting systolic and diastolic blood pressures at trough after eight weeks treatment were statistically significantly reduced for all active treatment arms versus placebo. Furthermore, the difference of the combination for sitting diastolic blood pressure was statistically significant in favour of the combination for both monotherapies. The incidence of treatment emergent adverse events did not differ significantly between groups: 32.5% with moxonidine, 25% with HCT, 30% with the combination and 23% with placebo.

Table 3: Reductions in sitting systolic/diastolic blood pressures at trough (intent-to-treat)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>Blood Pressure Reduction*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>P value</td>
</tr>
<tr>
<td>Placebo</td>
<td>41</td>
<td>-11.3</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>38</td>
<td>-19.4</td>
</tr>
<tr>
<td>HCT</td>
<td>40</td>
<td>-22.6</td>
</tr>
<tr>
<td>Combination</td>
<td>42</td>
<td>-25.9</td>
</tr>
</tbody>
</table>

*Least square mean change versus placebo

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In humans, about 90% of an oral dose of moxonidine is absorbed; it is not subject to first-pass metabolism and its bioavailability is 88%. Food intake does not interfere with moxonidine pharmacokinetics.

The maximum plasma levels of moxonidine are reached 30 – 180 minutes after the intake of a film-coated tablet.

Distribution

Only about 10% of moxonidine is bound to plasma proteins ($V_{dss}$=1.8±0.4 L/kg).
Metabolism
Moxonidine is 10 – 20% metabolised, mainly to 4,5-dehydromoxonidine and to a guanidine derivative by opening of the imidazoline ring. The hypotensive effect of 4,5-dehydromoxonidine is only 1/10, and that of the guanidine derivative is less than 1/100 of that of moxonidine.

Excretion
Moxonidine and its metabolites are eliminated almost entirely via the kidneys. More than 90% of the dose is eliminated via the kidneys in the first 24 hours after administration, while only about 1% is eliminated via the faeces. The cumulative renal excretion of unchanged moxonidine is about 50 – 75%.

The mean plasma elimination half-life of moxonidine is 2.2 – 2.3 hours, and renal elimination half-life is 2.6 – 2.8 hours. Although moxonidine has a relatively short half-life it should be administered no more frequently than twice daily.

Pharmacokinetics in the elderly
In older patients, the exposure (AUC) to moxonidine increased by approximately 50% following a single dose and at steady state, therefore lower doses of moxonidine should be used for the treatment of hypertension (see Section 4.3 Contraindications).

Pharmacokinetics in renal impairment
In moderately impaired renal function (GFR 30 – 60 mL/min), AUC increases by 85% and clearance decreased to 52%. In such patients the hypotensive effect of moxonidine should be closely monitored, especially at the start of treatment (see Section 4.2 Dose and method of administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Moxonidine did not induce gene mutations in bacteria or mammalian cells in vitro. Nor did it induce chromosomal aberrations in human lymphocytes in vitro or in Chinese hamster bone marrow cells in vivo.

Carcinogenicity
Carcinogenicity studies in rats and mice at oral doses of up to 3.6 mg/kg (rat) and 7.4 mg/kg (mouse) did not reveal evidence of carcinogenic potential. Systematic exposures at the highest dose were approximately 3 (rats, based on plasma moxonidine concentration) and 63 (mice, based on and dose adjusted for body surface area) times the clinical exposure at 0.3 mg BID.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
The tablets also contain the following excipients: lactose monohydrate, povidone, crospovidone, magnesium stearate, hypromellose, ethylcellulose, macrogol 6000, purified talc, iron oxide red and titanium dioxide.

6.2 INCOMPATIBILITIES
Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.
6.4 **SPECIAL PRECAUTIONS FOR STORAGE**

Physiotens tablets should be stored at or below 25°C.

6.5 **NATURE AND CONTENTS OF CONTAINER**

Physiotens 0.2 mg tablets: Packs of 7 tablets (sample), *10 tablets, *14 tablets, *28 tablets, 30 tablets, *56 tablets, *84 tablets, and *98 tablets.


*Products not currently marketed in Australia.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 **PHYSICOCHEMICAL PROPERTIES**

**Chemical Structure**


![Chemical Structure Diagram]

**CAS Number**

75438-57-2

7 **MEDICINE SCHEDULE (POISONS STANDARD)**

S4 (Prescription Only Medicine)

8 **SPONSOR**

Mylan Health Pty Limited

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

Australia


Phone: 1800 314 527
9 DATE OF FIRST APPROVAL

PHYSIOTENS moxonidine 200 microgram tablet blister pack: 10th November 2004
PHYSIOTENS moxonidine 300 microgram tablet blister pack: 10th November 2004
PHYSIOTENS moxonidine 400 microgram tablet blister pack: 10th November 2004

10 DATE OF REVISION

31 January 2019

Summary Table of Changes

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of New Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Reformatted according to new Australian PI template</td>
</tr>
<tr>
<td>4.4 Special warnings and precautions for use</td>
<td>Additional safety information regarding renal impairment</td>
</tr>
<tr>
<td>4.5 Interactions with other medicines and other forms of interactions</td>
<td>Clarification on safety use of PHYSIOTENS with other drugs</td>
</tr>
<tr>
<td>4.9 Overdose</td>
<td>Addition of overdose symptoms</td>
</tr>
<tr>
<td>10 Date of Revision</td>
<td>Updated from 18 September 2017 to 31 January 2019</td>
</tr>
</tbody>
</table>

Version 6