

# **NEW ZEALAND DATA SHEET**

## **1. ATENOLOL-AFT ORAL SOLUTION**

Atenolol-AFT, oral solution 50 mg/10 mL

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Atenolol-AFT: 50mg of atenolol per 10 mL of solution.

### Excipients with known effect:

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Oral solution.

Atenolol-AFT, oral solution is a clear, colourless, slightly viscous liquid with a lemon-lime odour and flavour which contains 50 mg Atenolol per 10 mL of solution.

While literature suggests that atenolol as an oral liquid behaves in the same way as atenolol tablets, no data directly comparing the bioavailability of Atenolol-AFT with atenolol tablets is available. Dose titration should be undertaken in a controlled manner and patients changing from the tablets to the oral liquid (or vice versa) should be monitored with the dosage being adjusted as appropriate.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

- Management of hypertension.
- Management of angina pectoris.
- Management of cardiac arrhythmias.
- Management of myocardial infarction. Early intervention in the acute phase and long term prophylaxis after recovery

### **4.2 Dose and method of administration**

While literature suggests that atenolol as an oral liquid behaves in the same way as atenolol tablets, no data directly comparing the bioavailability of Atenolol-AFT with atenolol tablets is available. Dose titration should be undertaken in a controlled manner and patients changing from the tablets to the oral liquid (or vice versa) should be monitored with the dosage being adjusted as appropriate.

Given the possibility of more calibrated dose titration with an oral solution, it may be appropriate to initiate doses at less than 50 mg. However, this would require an individual risk benefit assessment to be undertaken before any such decision.

#### Adults

##### *Hypertension*

Therapy should be initiated with 50 mg (10 mL) of Atenolol-AFT daily increasing up to 100 mg (20 mL) daily. Most patients respond to 50-100 mg (10-20 mL) given daily as a single dose. Where patients are controlled on daily doses of 50 - 100 mg (10-20 mL), this may be given once daily. The effect will be fully

established after 1-2 weeks. A further reduction in blood pressure may be achieved if necessary by combining atenolol with other antihypertensive agents.

#### *Angina Pectoris*

Therapy should be initiated with 50 mg (10 mL) of Atenolol-AFT daily. This may be increased to 100 mg (20 mL) daily (if required), given as a single or divided dose. It is unlikely that additional benefit will be gained by increasing the dose further.

#### *Cardiac Dysrhythmias*

Having controlled the dysrhythmias with intravenous agents, Atenolol-AFT given orally at a dosage of 50 - 100 mg (10-20 mL) daily will help maintain control.

#### *Myocardial Infarction*

For patients suitable for treatment with intravenous beta-blockade and presenting within 12 hours of the onset of chest pain, atenolol 5–10 mg should be given by slow intravenous injection (1 mg/minute) followed by atenolol 50 mg (10 mL) orally about 15 minutes later, provided no untoward effects have occurred from the intravenous dose. This should be followed by a further 50 mg (10 mL) orally 12 hours after the intravenous dose, and then 12 hours later by 100 mg (20 mL) orally, once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, atenolol should be discontinued.

#### *Impaired Renal Function*

Because atenolol is excreted via the kidneys, the dosage should be adjusted in cases of severe impairment of renal function.

No significant accumulation of atenolol occurs at a creatinine clearance greater than 35 mL/min/1.73m<sup>2</sup> (normal range is 100 to 150 mL/min/1.73m<sup>2</sup>. For patients with a creatinine clearance of 15 - 35 mL/min/1.73m<sup>2</sup> (equivalent to serum creatinine of 300 - 600 µmol/L) the dose should be 50 mg (10 mL) daily or 100 mg (20 mL) on alternate days. For patients with a creatinine clearance of less than 15 mL/min/1.73m<sup>2</sup> (equivalent to serum creatinine > 600 µmol/L) the dose should be 25 mg daily (5 mL), 50 mg (10 mL) on alternate days or 100 mg (20 mL) every fourth day.

Patients on haemodialysis should be given 50 mg (10 mL) after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

#### *Elderly*

Dosage requirements may be reduced especially in patients with impaired renal function.

#### *Children*

There is no experience with Atenolol-AFT in children

### **4.3 Contraindications**

- Known hypersensitivity to atenolol, or any of the other ingredients (see Further Information).
- Bronchospasm. Beta-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airway resistance. These medicines also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients. Therefore, beta-blockers are contraindicated in any patient with a history of airways obstruction or tendency to bronchospasm. Use of cardioselective beta-blockers can also result in severe bronchospasm. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.
- Congestive heart failure.

- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm.
- Right ventricular failure secondary to pulmonary hypertension.
- Significant right ventricular hypertrophy.
- Sick sinus syndrome.
- Sinus bradycardia (less than 45 to 50 beats/minute).
- Second and third degree A-V block.
- Shock (including cardiogenic and hypovolaemic shock).
- Anaesthesia with agents that produce myocardial depression (eg. ether, chloroform, cyclopropane).
- Hypotension.
- Metabolic acidosis.
- Severe peripheral arterial circulatory disturbances.
- Untreated phaeochromocytoma.
- Pregnancy and lactation (see “Warnings and Precautions – Use in Pregnancy and Lactation”).

#### **4.4 Special warnings and precautions for use**

No data directly comparing the bioavailability of Atenolol-AFT with atenolol tablets is available. While it is expected that the tablets and liquid will behave in the same manner, dose titration with the oral liquid should be undertaken in a controlled manner and patients changing from the tablets to the oral liquid (or vice versa) should be monitored with the dosage being adjusted as appropriate.

##### *Cardiac Failure*

$\beta$ -blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency or unsuspected cardiomyopathy as may occur in chronic alcoholism. In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If signs of cardiac failure present, the patients should be fully digitalised and/or given an ACE inhibitor or vasodilators with or without a diuretic and carefully monitored. If cardiac failure persists, the beta-blocker should be withdrawn. See Precautions – Abrupt withdrawal of therapy.

Note: Although congestive heart failure has been considered to be a contraindication to the use of  $\beta$ -blockers, there is growing literature on the experimental use of  $\beta$ -adrenergic blocking drugs in heart failure. As further trials are needed to identify which patients are most likely to respond to which drugs,  $\beta$ -blockers should not normally be prescribed for heart failure outside of specialist centres.

##### *Abrupt Withdrawal of Therapy*

Care should be taken if  $\beta$ -blockers have to be discontinued abruptly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of  $\beta$ -blockade in patients with ischaemic heart disease. It is recommended that the dosage be reduced gradually over a period of about 8 - 14 days during which time the patient's progress should be reassessed. The drug may be reinstated temporarily if the angina worsens. If the drug must be withdrawn abruptly, close observation is required. In the peri-operative period,  $\beta$ -blockers should not be withdrawn, unless indicated.

##### *History of Anaphylactic Reaction*

While taking  $\beta$ -adrenoreceptor blocking drugs, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge. These patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

#### *First Degree Heart Block*

Caution must be exercised if atenolol is given to patients with first degree heart block because of its negative effect on conduction time.

#### *Peripheral Circulation*

$\beta$ -blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease.

#### *Prinzmetal Angina*

If patients with Prinzmetal or variant angina are treated with a  $\beta$ -blocker, there is a risk of exacerbating coronary artery spasm. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

#### *Euthyroid Hyperthyroxinaemia*

The effects of  $\beta$ -blockers on thyroid hormone metabolism may result in elevation of serum free thyroxine (T4) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

#### *Use in Acute Myocardial Infarction*

In addition to the contraindications listed above, patients with the following conditions are not suitable for treatment with atenolol:

- Systolic blood pressure less than 120 mmHg (systolic blood pressure < 120 mmHg in combination with a heart rate > 90 beats/min has a particularly poor prognosis).
- First degree A-V block. There is an increased incidence of cardiogenic shock (and need for inotropes), complete heart block and cardiovascular death in these patients, following atenolol administration.

Patients with atrial fibrillation following myocardial infarction treated with atenolol, had increased cardiovascular mortality when compared with those not treated with atenolol. It is recommended that such patients be digitalised before atenolol therapy is begun.

#### *Bradycardia*

If a treated patient develops symptoms which may be attributable to a slow heart rate, the dose may be reduced.

#### *Anaesthesia and the Peri-operative Period*

$\beta$ -blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the post-operative period. It is currently recommended that maintenance of  $\beta$ -blockade be continued peri-operatively. The anaesthetist must be advised of the  $\beta$ -blockade due to the potential for interactions with other drugs which may result in severe bradyarrhythmias and hypotension, decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and an increased propensity for vagal-induced bradycardia. Incidents of protracted severe hypotension or of difficulty in restoring normal cardiac rhythm during anaesthesia have been reported. Modern inhalational anaesthetic agents are generally well tolerated, however older agents e.g. ether, cyclopropane, methoxyflurane, trichlorethylene have been associated with severe circulatory depression in the presence of  $\beta$ -blockade.

### *Diabetes*

$\beta$ -blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, e.g. tachycardia. In patients with insulin or non-insulin dependent diabetes (especially labile diabetes), or with a history of spontaneous hypoglycaemia,  $\beta$ -blockade may result in the loss of diabetic control and delay recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need to be adjusted.

### *Other Metabolic Effects*

$\beta$ -adrenoreceptors are involved in the regulation of lipid and carbohydrate metabolism. While some drugs affect the lipid profile adversely, the long-term clinical significance of this change is unknown and the effect appears to be less for drugs with intrinsic sympathomimetic activity.

### *Phaeochromocytoma*

In patients with this condition, an  $\alpha$ -blocking drug e.g. phentolamine, phenoxybenzamine should be administered before the  $\beta$ -blocker to avoid exacerbation of hypertension.

### *Eye and Skin Reactions*

Skin rashes and conjunctival xerosis have been reported with  $\beta$ -blockers. Cross-reactions may occur between  $\beta$ -blockers, therefore, substitutions within the group may not necessarily preclude occurrence of symptoms.

During long-term treatment with the  $\beta$ -blocker practolol, a rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of patients, this rash was accompanied by adverse effects on the eye (xerophthalmia and/or keratoconjunctivitis) of varying severity. This condition is called the oculomucocutaneous syndrome or practolol syndrome. In a few patients, these eye changes occurred without a skin rash. On rare occasions, serous otitis media, sclerosing peritonitis, pericarditis and pleurisy have been reported. Although the practolol syndrome has not been observed in patients taking other  $\beta$ -blockers, the possibility of such side effects occurring should be kept in mind.

More recently an association between Peyronie's disease and various  $\beta$ -blockers has been suggested but is not proven.

### *Allergic Conditions*

Allergic reactions e.g. allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings may be exaggerated by  $\beta$ -blockade.  $\beta$ -blockers should be avoided if there is a risk of bronchospasm.

### *Hyperthyroidism*

$\beta$ -blockers may mask the clinical signs of developing or continuing hyperthyroidism, resulting in symptomatic improvement without any change in thyroid hormone status. Caution should be exercised in those patients who are hyperthyroid and also receiving  $\beta$ -blockers.

### *Renal Disease*

In patients with severe renal disease, haemodynamic changes following  $\beta$ -blockade may further impair renal function.  $\beta$ -blockers which are excreted mainly by the kidney may require dose adjustment in patients with renal failure.

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

### *Calcium Antagonists*

The concomitant use of  $\beta$ -blockers and calcium antagonists with myocardial depressant and sinus node activity e.g. verapamil and, to a lesser extent, diltiazem, may cause hypotension, bradycardia and asystole, particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. Extreme caution is required if these drugs are to be used together.

The dihydropyridine calcium antagonists e.g. nifedipine have a weaker myocardial depressant effect and can be administered cautiously with  $\beta$ -blockers. If excessive hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

#### *Antiarrhythmic Drugs*

Class 1 anti-arrhythmic drugs e.g. disopyramide and the Class III agent, amiodarone may have potentiating effect on atrial conduction time and induce negative inotropic effect. This is seen less frequently with quinidine; Class IB agents, tocainide, mexiletine and lignocaine; Class IC agents, flecainide and the Class IV antiarrhythmic agents.

#### *Catecholamine-Depleting Agents*

Concomitant use of drugs such as reserpine and guanethidine requires careful monitoring because the added effect of  $\beta$ -blockade may produce an excessive reduction of the resting sympathetic nervous tone.

#### *Clonidine*

Concurrent use of  $\beta$ -blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the  $\beta$ -blocker.

#### *Insulin and oral hypoglycaemics*

See Precautions – Diabetes above

#### *Anaesthetics*

Anaesthetics e.g. methoxyflurane are contraindicated with Atenolol-AFT. See Precautions – Anaesthesia and the Peri-operative Period.

#### *Digitalis / digitalis glycosides*

Digitalis/digitalis glycosides and  $\beta$ -blockers are commonly used together, although there have been reports of excessive bradycardia when  $\beta$ -blockers are used to treat digitalis intoxication.

#### *Sympathomimetic agents*

Concomitant use of sympathomimetic agents e.g. adrenaline may counteract the effects of  $\beta$ -blockers.

#### *Prostaglandin synthetase inhibitors*

Concomitant use of prostaglandin synthetase inhibiting drugs, e.g. ibuprofen and indomethacin may decrease the hypotensive effects of  $\beta$ -blockers.

### **4.6 Fertility, pregnancy and lactation**

#### *Category C.*

$\beta$ -blockers may cause bradycardia in the foetus and newborn infant. During pregnancy and parturition, these drugs should only be given after weighing the potential benefit to the mother against the potential risk to the foetus.

Atenolol crosses the placental barrier in pregnant women and appears in the cord blood. Under steady-state conditions, maternal and foetal blood levels of atenolol are approximately equal.

No studies have been performed on the use of atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation.

The use of atenolol in women who are, or may become pregnant, requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters as  $\beta$ -blockers have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Atenolol has been shown to produce a dose-related increase in embryo/foetal resorptions in rats at doses equal to or greater than 50 mg/kg. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg.

#### Use in Lactation

There is a significant accumulation of atenolol in breast milk. Caution should be exercised when atenolol is administered to nursing women and the infant should be regularly assessed for signs of  $\beta$ -blockade.

#### **4.7 Effect on ability to drive and use machines**

Any impairment of the ability of patients to drive or operate machinery is unlikely, however dizziness or fatigue may occur occasionally.

#### **4.8 Undesirable effects**

Atenolol is generally well tolerated. Adverse reactions reported in clinical studies were mainly attributable to pharmacological actions. The adverse reactions listed below have been observed in patients in clinical trials who have received dosages of about 100 mg per day. It is not possible to give percentage incidences for each reaction, but if all mild and transient reactions are included as well as the more serious ones, up to 10% of patients may experience some form of adverse reaction.

<b>More Common Reactions</b>	
Gastrointestinal	Dry mouth, gastrointestinal disturbance including indigestion, constipation
Nervous System	Fatigue, Dizziness
Respiratory	Wheezing, bronchospasm (See Contraindications)
<b>Less Common Reactions</b>	
Biochemical Abnormalities	Increases in SGOT, blood urea and serum creatinine have been reported
Cardiovascular	Bradycardia, left ventricular insufficiency, postural hypotension which may be associated with syncope, intermittent claudication may occur if already present, Raynaud's phenomenon, cold extremities, deterioration in heart failure, heart block
Dermatological	Rash, alopecia, psoriasisiform skin reactions, exacerbation of psoriasis
Gastrointestinal	Diarrhoea, elevations of transaminase levels have been seen infrequently, rare cases of hepatic toxicity including intrahepatic cholestasis have been reported
Genito-Urinary	Impotence
Musculo-Skeletal	Ataxia
Nervous System	Vivid dreams, nightmares, paraesthesia, tinnitus, vertigo, malaise, headache, insomnia, mood changes, confusion
Ocular	Dry eyes, visual disturbances
Psychiatric	Hallucinations, depression, psychoses
Respiratory	Asthma, dyspnoea, nasal congestion
Haemopoietic	Thrombocytopenia, purpura. An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.

#### Serious or Life-Threatening Reactions

Myocardial insufficiency may require treatment with digitalis and diuretics. Bradycardia may respond to atropine. Bronchospasm may be reversed with a  $\beta_2$ - stimulant. Hypotension, if severe, may require use of a vasopressor.

#### **4.9 Overdose**

Contact the Poisons Information Centre (0800 POISON, 0800 764766) for advice. While overdosage has not been reported with atenolol, in overdosage with other  $\beta$ -blocking agents, severe bradycardia and hypotension are commonly found. Acute heart failure and bronchospasm may also occur.

#### Management

*Severe bradycardia*

Atropine, 1 - 2 mg I.V. may be used to induce vagal blockade. If bradycardia persists, an inotrope e.g. intravenous isoprenaline (25 µg initially) may be given. In refractory cases, the use of a cardiac pacemaker may be considered.

#### *Hypotension*

Severe hypotension should respond to a sympathomimetic amine e.g. noradrenaline. In refractory cases, the use of glucagon hydrochloride should be considered.

#### *Bronchospasm*

Therapy with a β2-stimulant e.g. salbutamol or terbutaline or therapy with aminophylline may be considered.

#### *Acute Cardiac Failure*

Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases, the use of intravenous isoprenaline followed by glucagon hydrochloride or intravenous aminophylline if necessary should be considered.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Atenolol is a β-adrenoreceptor blocking drug which acts preferentially on β1-receptors in the heart. Selectivity decreases with increasing dose. It has little intrinsic sympathomimetic activity and no membrane stabilising activity. Atenolol is a racemic mixture with the activity in the S(-) enantiomer. It reduces raised blood pressure by an unknown mechanism, inhibits exercise induced tachycardia and decreases plasma renin concentration. It causes slight airway obstruction but less than that seen with non-selective β-blockers. The inhibition of exercise induced tachycardia is correlated with blood levels but there is no correlation between plasma concentrations and antihypertensive effect.

Atenolol is effective and well tolerated in most ethnic populations although the response may be less in Afro-Caribbean black patients.

The possible mechanism of the anti-anginal activity of atenolol appears to be due to a reduction in left ventricular work and oxygen utilisation as a result of the decrease in heart rate and contractility.

The anti-arrhythmic effect of atenolol is apparently due to its anti-sympathetic effect. There is no evidence that membrane stabilising activity or intrinsic sympathomimetic activity are necessary for anti-arrhythmic efficacy. Atenolol depresses sinus node function, atrioventricular node function and prolongs atrial refractory periods. It has no direct effect on electrophysiological properties of the HIS-purkinje system.

β-adrenoreceptor blocking agents should be avoided in uncontrolled heart failure because of their negative inotropic effects.

### **5.2 Pharmacokinetic properties**

#### Absorption

Although absorption of atenolol is variable and incomplete (40 to 60%) the virtual lack of hepatic metabolism results in a relatively consistent systemic bioavailability compared to other β-blockers. Blood levels in humans peak 2 - 4 hours after a single 100 mg oral dose and are typically 0.4 - 0.9 µg/mL. Blood levels are consistent and the levels after chronic oral administration are in good agreement with those predicted from single dose results.

#### Distribution

Atenolol is distributed throughout the body tissues.

#### Metabolism

Less than 10% of a dose is metabolised. The minor urinary metabolite has been identified as a hydroxylated derivative.

#### Excretion

The main route of elimination is renal excretion.

#### Half-Life

The plasma half-life, measured by blood level decay or urinary build up, is approximately 7 - 9 hours. In patients with impaired renal function there is a progressive prolongation of the half-life.

In patients with normal kidney function, the therapeutic effect lasts for not less than 24 hours after a 50 mg oral dose.

While literature suggests that atenolol as an oral liquid behaves in the same way as atenolol tablets, no data directly comparing the bioavailability of Atenolol-AFT with atenolol tablets is available. Dose titration should be undertaken in a controlled manner and patients changing from the tablets to the oral liquid (or vice versa) should be monitored with the dosage being adjusted as appropriate.

#### Other

Atenolol is a racemic mixture which has the chemical name 2-[4-[(2RS)-2-hydroxy-3-[(1-methylethyl)amino] propoxy] phenyl] acetamide. It has the chemical formula C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> with a molecular weight of 266.3. The CAS number is 29122-68-7.

Atenolol-AFT, oral solution also contains sorbitol solution (70 per cent) (non-crystallising), methyl hydroxybenzoate, propyl hydroxybenzoate, sodium saccharin, citric acid monohydrate, sodium citrate, propylene glycol and lemon lime flavour PHL0132956.

Sorbitol may have a laxative effect or cause diarrhoea.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Other excipient

Citric acid monohydrate 1.85mg/mL, Lemon flavour 11903-56 0.25mg/mL, Propylene glycol 52mg/mL, purified water q.s, saccharin sodium 0.06mg/mL, sodium citrate 3.53mg/mL, sorbitol 452.6mg/mL

#### Other excipient, preservative

Methyl hydroxybenzoate 2mg/mL, Propyl hydroxybenzoate 0.2mg/mL

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

18 months from date of manufacture stored at or below 25°C.

#### **6.4 Special precautions for storage**

Store below 25 °C. Store in the original carton to protect from light.

Use within 1 month of opening.

#### **6.5 Nature and contents of container**

Atenolol-AFT, oral solution is available in PET bottles which contain 300 mL.

#### **6.6 Special precautions for disposal**

No special requirements.

### **7. MEDICINE SCHEDULE**

Prescription medicine.

### **8. SPONSOR**

AFT Pharmaceuticals Ltd

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### **9. DATE OF FIRST APPROVAL**

27 February 2014

### **10. DATE OF REVISION OF THE TEXT**

February 2019

### **SUMMARY TABLE OF CHANGES**

Date	Section(s) Changed	Change (s)
February 2019	All	Reformat consistent with new Medsafe Data Sheet Template.