

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

ARROW - DORTIM

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6.83 mg of timolol maleate).

Excipient of known effect: benzalkonium chloride

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Eye drops, solution. The solution is a clear, colourless slightly viscous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ARROW – DORTIM is indicated for the treatment of elevated intraocular pressure (IOP) in patients with:

- ocular hypertension
- open-angle glaucoma
- pseudoexfoliative glaucoma
- or other secondary open-angle glaucoma's

and who are:

- insufficiently responsive to topical beta blocker monotherapy
- currently receiving concomitant antiglaucoma therapies such as dorzolamide hydrochloride and timolol maleate

### 4.2 Dose and method of administration

#### Dose

The dose is one drop of ARROW-DORTIM in the affected eye(s) two times daily. When substituting ARROW-DORTIM for another ophthalmic antiglaucoma agent(s), discontinue the other agent(s) after proper dosing on one day, and start ARROW-DORTIM on the next day.

#### **Paediatric population**

Safety and efficacy in paediatric patients below the age of 2 years have not been established. (For information regarding use in paediatric patients  $\geq 2$  years of age see **section 4.4 Special warnings and precautions for use, Paediatric Use**).

#### Method of administration

If another topical ophthalmic agent is being used, ARROW-DORTIM and the other agent should be administered at least ten minutes apart.

Use with contact lenses: The contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes (see **4.4 Special warnings and precautions for use**).

### 4.3 Contraindications

ARROW-DORTIM is contraindicated in patients with:

- reactive airway disease, bronchial asthma or other obstructive lung disorders or a history of bronchospasm

- uncontrolled heart failure (see 4.4 **Special warnings and precautions for use**)
- cardiogenic shock
- sick sinus syndrome
- grade 2 and 3 AV block and infranodal AV block
- severe bradycardia
- hypersensitivity to any component of this product
- sino-atrial block

The above are based on the components and are not unique to the combination.

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

As with other topically-applied ophthalmic agents, this medicine may be absorbed systemically. The timolol component is a beta-blocker. Therefore, the same types of adverse reactions found with systemic administration of beta-blockers may occur with topical administration.

##### **Cardio-respiratory Reactions**

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with ARROW-DORTIM. Patients with a history of cardiovascular disease, including cardiac failure should be watched for signs of deterioration of these diseases and pulse rates should be checked.

Due to its negative effect on conduction time, beta-blockers should be given with caution to patients with first degree heart block.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate ophthalmic solution.

In patients with mild/moderate chronic obstructive pulmonary disease (COPD), ARROW-DORTIM should be used with caution, and only if the potential benefit outweighs the potential risk.

##### **Vascular Disorders**

Patients with severe peripheral circulatory disturbance/disorders (e.g. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

##### **Renal and Hepatic Impairment**

ARROW-DORTIM has not been studied in patients with severe renal impairment ( $\text{CrCl} < 30$  millilitre/min). Because dorzolamide hydrochloride and its metabolite are excreted predominantly by the kidney, ARROW-DORTIM is not recommended in such patients.

ARROW-DORTIM has not been studied in patients with hepatic impairment and therefore should be used with caution in such patients.

##### **Immunology and Hypersensitivity**

As with other topically-applied ophthalmic agents, this medicine may be absorbed systemically. The dorzolamide component is a sulphonamide. Therefore, the same types of adverse reactions found with systemic administration of sulphonamides may occur with topical administration, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of dorzolamide hydrochloride ophthalmic solution. Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of medicine therapy. Similar reactions have been reported with dorzolamide hydrochloride and timolol maleate ophthalmic solution. If such reactions are observed,

discontinuation of treatment with dorzolamide hydrochloride and timolol maleate ophthalmic solution should be considered.

While taking  $\beta$ -blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to accidental, diagnostic, or therapeutic repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

### **Concomitant Therapy**

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving oral and topical carbonic anhydrase inhibitors concomitantly. The concomitant administration of ARROW-DORTIM and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Patients who are already receiving a beta-adrenergic blocking agent systemically and who are given ARROW-DORTIM should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade. The use of two topical beta-adrenergic blocking agents is not recommended.

### **Other**

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. ARROW-DORTIM has not been studied in patients with acute angle-closure glaucoma.

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide, dorzolamide) after filtration procedures.

There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing ARROW-DORTIM to this group of patients.

There have been reports of bacterial keratitis associated with the use of multidose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patient should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infection. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should be advised that if they develop an intercurrent ocular condition (eg. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

### **Contact Lens Use**

ARROW-DORTIM contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, ARROW-DORTIM should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

### **Paediatric Use**

Studies in children aged between 2 to 6 years of age indicate that the product is generally well tolerated however, it should be used with precaution in children of this age group.

Dorzolamide has not been studied in patients less than 36 weeks gestational age and less than 1 week of age. Patients with significant renal tubular immaturity should only receive dorzolamide after careful consideration of the risk benefit balance because of the possible risk of metabolic acidosis

### **Systemic Effects of Beta-Adrenergic Blocking Agents**

#### *Cardiac Failure*

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In patients without a history of cardiac failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure ARROW-DORTIM should be discontinued.

#### *Surgical Anesthesia*

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

#### *Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus*

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycaemia.

#### *Masking of Thyrotoxicosis*

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g. tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

#### *Muscle Weakness*

Beta-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

#### *General*

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with ARROW-DORTIM, alternative therapy should be considered.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product (see **section 4.3 Contraindications**).

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

Specific medicine interaction studies have not been performed with ARROW-DORTIM.

In clinical studies, dorzolamide hydrochloride and timolol maleate ophthalmic solution was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory medicines including aspirin, and hormones (e.g., oestrogen, insulin, thyroxine).

However, the potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium

channel blockers, catecholamine-depleting medicines, antiarrhythmics, parasympathomimetics or beta-adrenergic blocking agents.

Potentiating systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, SSRIs) and timolol.

The dorzolamide component of ARROW-DORTIM is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically.

In clinical studies, dorzolamide hydrochloride ophthalmic solution was not associated with acid-base disturbances. However, these disturbances have been reported with oral carbonic anhydrase inhibitors and have in some instances, resulted in medicine interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such medicine interactions should be considered in patients receiving ARROW-DORTIM.

Oral  $\beta$ -adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two medicines are co-administered, the  $\beta$ -adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by  $\beta$ -blocker therapy, the introduction of  $\beta$ -adrenergic blocking agents should be delayed for several days after clonidine has stopped.

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

##### **Pregnancy**

There are no adequate and well-controlled studies in pregnant women. ARROW-DORTIM should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

##### **Lactation**

It is not known whether dorzolamide hydrochloride is excreted in human milk. Timolol maleate does appear in human milk. Because of the potential for serious adverse reactions on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the medicine, taking into account the importance of the medicine to the mother.

##### **Fertility**

No information available.

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

There are adverse effects associated with ARROW-DORTIM that may affect some patients' ability to drive and/or operate machinery. (see **4.8 Undesirable effects**)

#### **4.8 Undesirable effects**

In clinical studies, dorzolamide hydrochloride and timolol maleate ophthalmic solution was generally well tolerated; no adverse experiences peculiar to this combination medicine have been observed. Adverse experiences have been limited to those that were reported previously with dorzolamide hydrochloride and/or timolol maleate. In general, common adverse experiences were mild and did not cause discontinuation.

During clinical studies, 1035 patients were treated with dorzolamide hydrochloride and timolol maleate ophthalmic solution. Approximately 2.4% of all patients discontinued therapy with dorzolamide hydrochloride and timolol maleate ophthalmic solution because of local ocular adverse reactions, approximately 1.2% of all patients discontinued because of local adverse reactions suggestive of allergy or hypersensitivity.

The most frequently reported medicine-related adverse effects were: ocular burning and stinging, taste perversion, corneal erosion, conjunctival injection, blurred vision, tearing and ocular itching. Urolithiasis was reported rarely.

The following adverse reactions have been reported in post-marketing experience: dyspnoea, respiratory failure, contact dermatitis, bradycardia, heart block, choroidal detachment following filtration surgery, nausea, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Additional adverse effects that have been seen with one of the components and may be potential adverse effects of ARROW-DORTIM are:

### **Dorzolamide Hydrochloride**

Headache; eyelid inflammation; nausea; eyelid irritation; eyelid crusting; asthenia/fatigue; iridocyclitis; rash; dizziness; paresthesia, transient myopia (which resolved upon discontinuation of therapy); local reaction including palpebral reactions and signs and symptoms of systemic allergic reactions including angioedema, bronchospasm, urticaria and pruritus, epistaxis, contact dermatitis, throat irritation, dry mouth.

### *Paediatric Patients*

In a clinical trial with 184 paediatric patients the adverse event profile of dorzolamide hydrochloride was comparable to that seen in adult patients. In this trial approximately 20% of patients had a medicine-related adverse event, the majority of which were local, non-serious ocular effects such as burning stinging, injection and eye pain. A small percentage of patients in this trial (<4%) were observed to have corneal oedema or haze. Local reactions appeared similar in frequency to the comparator.

In post marketing data, metabolic acidosis in the very young children particularly with renal immaturity / impairment has been rarely reported.

### **Timolol Maleate (topical formulation)**

Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, and decreased corneal sensitivity, dry eyes; visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, and ptosis; tinnitus; arrhythmia; hypotension; syncope; cerebrovascular accident; cerebral ischaemia; congestive heart failure; palpitation; cardiac arrest; oedema, claudication, Raynaud's phenomenon, cold hands and feet; bronchospasm (predominantly in patients with pre-existing bronchospastic disease); cough; headache; asthenia; fatigue; chest pain; alopecia, psoriasiform rash or exacerbation of psoriasis; signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash; dizziness; depression, insomnia, nightmares, memory loss; increase in signs and symptoms of myasthenia gravis, paresthesia; nausea, diarrhoea, dyspepsia, dry mouth; decreased libido, Peyronie's disease; systemic lupus erythematosus.

### **Laboratory Findings**

ARROW-DORTIM was not associated with clinically meaningful electrolyte disturbances in clinical studies.

### **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/>).

### **4.9 Overdose**

No data are available with regard to human overdosage by accidental or deliberate ingestion of ARROW-DORTIM.

There have been reports of inadvertent overdosage with timolol maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. The most

common signs and symptoms to be expected with overdose of dorzolamide are electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects.

Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

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

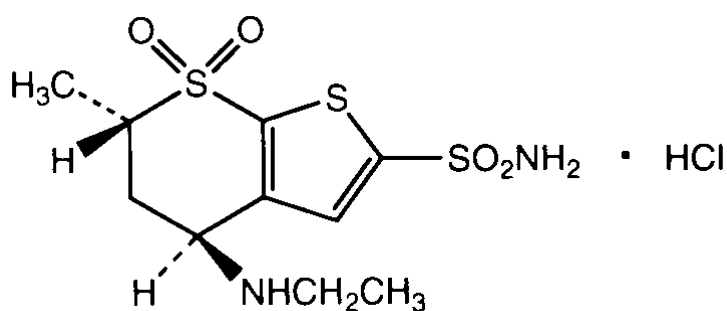
Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking agents, Timolol, combinations, ATC code: S01ED51

ARROW-DORTIM is a combination of a topical carbonic anhydrase inhibitor, dorzolamide hydrochloride, and a topical beta-adrenergic receptor blocking agent, timolol maleate.

#### Dorzolamide Hydrochloride

Dorzolamide hydrochloride is described chemically as: (4 S- trans)-4-(ethylamino)-5,6-dihydro-6-methyl-4 H-thieno [2,3- b]thiopyran-2-sulphonamide 7,7-dioxide monohydrochloride.

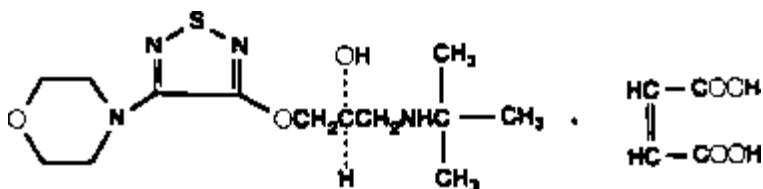
Its empirical formula is  $C_{10}H_{16}N_2O_4S_2HCl$  and its structural formula is:



Dorzolamide hydrochloride has a molecular weight of 360.91. It is a white to off-white, free flowing crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

#### Timolol Maleate

Timolol maleate is described chemically as: ( S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol,( Z)-2-butenedioate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in the structure and is provided as the levoisomer. The empirical formula is  $C_{13}H_{24}N_4O_5S$  and the structural formula is:



Timolol maleate has a molecular weight of 432.50. It is a white, odourless, crystalline powder which is soluble in water, methanol, and alcohol.

#### Mechanism of action

ARROW-DORTIM is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure by reducing aqueous humor secretion, but does so by a different mechanism of action.

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. The combined effect of these two agents results in additional intraocular pressure reduction compared to either component administered alone.

Following topical administration, ARROW-DORTIM reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. ARROW-DORTIM reduces intraocular pressure without the common adverse effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

## **5.2 Pharmacokinetic properties**

### **Dorzolamide Hydrochloride**

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the medicine to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure. In clinical trials, this resulted in a reduction in IOP without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors.

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, medicine and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while extremely low concentrations of free medicine in plasma are maintained. The parent medicine forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent medicine but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33%). Dorzolamide is primarily excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of medicine concentration initially, followed by a slower elimination phase with a half-life of about four months.

When dorzolamide was given orally to simulate the maximum systemic exposure after long term topical ocular administration, steady state was reached within 13 weeks. At steady state, there was virtually no free medicine or metabolite in plasma; CA inhibition in RBCs was less than that anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were observed after chronic, topical administration of dorzolamide hydrochloride. However, some elderly patients with renal impairment (estimated CrCl 30-60 millilitre/min) had higher metabolite concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic adverse effects were directly attributable to this finding.

### **Timolol Maleate**

In a study of plasma medicine concentration in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

## **5.3 Preclinical safety data**

*Animal Toxicology:*



The ocular and systemic safety profile of the individual components is well established. Furthermore, no adverse ocular effects were seen in animals treated topically with dorzolamide hydrochloride and timolol maleate ophthalmic solution or with concomitantly-administered dorzolamide hydrochloride and timolol maleate. Therefore, no significant risk for human safety is expected with therapeutic doses of ARROW-DORTIM.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Benzalkonium chloride 0.0075% (as preservative)

Sodium citrate

Hydroxyethylcellulose

Sodium hydroxide

Mannitol

Water for Injections

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

Before first opening: 2 years

After first opening of bottle: 4 weeks

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

Unopened: Store at or below 25°C. Protect from light.

After first opening the bottle: Do not store above 25°C and use within four weeks. Keep the bottle in the outer carton in order to protect from light.

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

LDPE bottle (5 mL) with insert-cap assembly comprising of a blue coloured screw cap over a LDPE nozzle with tamper-evident LDPE dustcover sealing the bottle cap.

Pack sizes: 1 x 5 mL

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

The tamper evident dustcover should be removed before use. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MEDICINE SCHEDULE**

Prescription Only Medicine

## **8. SPONSOR**

Teva Pharma (New Zealand) Limited

PO Box 128 244

Remuera

Auckland 1541

Telephone: 0800 800 097

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

2 May 2013

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

29 April 2019

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	New version