AUSTRALIAN PRODUCT INFORMATION
VERSATIS® (Lidocaine (Lignocaine)) 5% w/w Dermal Patch

1 NAME OF THE MEDICINE

Lidocaine (Lignocaine)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dermal patch (10 cm x 14 cm) contains 700 mg (5% w/w) lidocaine (lignocaine) (50 mg lidocaine per gram adhesive base).

Excipients with known effect: hydroxybenzoates.

For the full list of excipients, see Section **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

VERSATIS® is a white hydrogel patch containing adhesive material, which is applied to a non-woven polyethylene terephthalate backing embossed with 'Lidocaine 5%' and covered with a polyethylene terephthalate film release liner.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VERSATIS® is indicated for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (PHN).

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and elderly patients

The painful area should be covered with VERSATIS® once daily for up to 12 hours within a 24-hour period. Only the number of patches that are needed for an effective treatment should be used. When needed, the patches may be cut into smaller sizes with scissors prior to removal of the release liner. In total, not more than three patches should be used at the same time.

VERSATIS® must be applied to intact, dry, non-irritated skin (after healing of the shingles).

Each patch must be worn no longer than 12 hours. The subsequent patch-free interval must be at least 12 hours.

The patch must be applied to the skin immediately after removal from the sachet and following removal of the release liner from the gel surface. Hairs in the affected area must be cut off with a pair of scissors (not shaved).

Treatment outcome should be re-evaluated after 2–4 weeks. If there has been no response to VERSATIS® after this period or if any relieving effect can solely be related to the skin protective properties of VERSATIS®, treatment must be discontinued as potential risks may outweigh benefits in this context (see Section **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and Section **5.1 PHARMACODYNAMIC PROPERTIES**). Treatment should be reassessed at regular intervals to decide whether the number of patches needed to cover the painful area can be reduced, or if the patch-free period can be extended.

Use for patients under the age of 18 is not recommended because of the lack of data in this group.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. VERSATIS® is also contraindicated in patients with known hypersensitivity to other local anaesthetics of the amide type e.g. bupivacaine, etidocaine, mepivacaine and prilocaine.

VERSATIS® must not be applied to inflamed or injured skin, such as active herpes zoster lesions, atopic dermatitis or wounds.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

VERSATIS® should not be applied to mucous membranes. Eye contact with the patch should be avoided.

VERSATIS® contains propylene glycol which may cause skin irritation. It also contains methyl hydroxybenzoate and propyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

Excessive dosing

Excessive dosing by applying VERSATIS® to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and higher blood concentrations, which may lead to systemic adverse drug reactions (see Section **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients or impaired elimination may all contribute to increasing the blood concentration of lidocaine. Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 µg/mL. With recommended dosing of VERSATIS®, the average peak blood concentration is about 0.13 µg/mL, but individual concentrations up to 0.28 µg/mL have been observed in clinical trials.

Use in hepatic impairment

VERSATIS® should be used with caution in patients with severe hepatic impairment. The excretion of lidocaine and its metabolites may be delayed in patients with severe hepatic impairment. Higher systemic concentrations of lidocaine may occur.

Use in renal impairment

VERSATIS® should be used with caution in patients with severe renal impairment. The excretion of lidocaine and its metabolites may be delayed in patients with severe renal impairment. Higher systemic concentrations of lidocaine may occur.

Use in cardiac impairment

VERSATIS® should be used with caution in patients with severe cardiac impairment. The excretion of lidocaine and its metabolites may be delayed in patients with severe cardiac impairment. Higher systemic concentrations of lidocaine may occur.

Use in the elderly

Generally, no dosage adjustment is necessary for elderly patients (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric use

Use for patients under the age of 18 is not recommended because of the lack of data in this group.

Effects on laboratory tests

Laboratory findings did not give any indication for safety-relevant issues during clinical trials.

External heat sources

Placement of external heat sources, such as heating pads or electric blankets, over VERSATIS® is not recommended as this has not been evaluated and may increase plasma lidocaine levels.

Accidental exposure

Even a used VERSATIS® patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or pet to suffer serious adverse effects from chewing or ingesting a new or used VERSATIS® patch, although the risk with this formulation has not been evaluated. It is important for patients to store and dispose of VERSATIS® out of the reach of children, pets and others.

Lidocaine metabolite toxicity

The lidocaine metabolite, 2,6-xylidine, has been shown to be genotoxic and carcinogenic in rats and a secondary metabolite has been shown to be mutagenic (see Section **5.3 PRECLINICAL SAFETY DATA**). The clinical significance of these findings is unknown. Consequently, long-term treatment with VERSATIS® is only justified if there is a therapeutic benefit for the patient (see Section **4.2 DOSE AND METHOD OF ADMINISTRATION**).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed. No clinically relevant interactions have been observed in clinical studies with VERSATIS®.

Antiarrhythmic drugs

Although normally the absorption of lidocaine from the skin is low, VERSATIS® must be used with caution in patients receiving Class I antiarrhythmic medicinal products (e.g. tocainide, mexiletine) since the cardiac effects (including arrhythmia) and CNS effects (including convulsions, CNS depression) may be additive and potentially synergistic.

Local anaesthetic agents

When VERSATIS® is used concomitantly with other products containing local anaesthetic agents, the amount absorbed from all formulations must be considered.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No clinical data regarding fertility are available for lidocaine. Animal studies have not shown effects on female fertility.

Use in pregnancy – Pregnancy Category A

Lidocaine crosses the placenta. However, there are no adequate data from the use of lidocaine in pregnant women. Animal studies are incomplete with respect to effects on pregnancy, embryo fetal development, parturition or postnatal development.

Lidocaine had no effect on general reproductive performance in rats at plasma concentrations up to 130-fold of those observed in patients. No adverse effects were seen in an embryofetal/teratogenicity study in rats at plasma concentrations more than 200-fold of that observed in patients.

The potential risk for humans is unknown. Therefore, VERSATIS® should not be used during pregnancy unless clearly necessary.

Use in lactation

Lidocaine is excreted in milk. However, there are no studies of VERSATIS® in breastfeeding women. Since the metabolism of lidocaine is relatively rapid and almost completely in the liver, only very low levels of lidocaine are expected to be excreted into milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. An effect on the ability to drive and use machines is unlikely because systemic absorption is minimal (see Section **5.2 PHARMACOKINETIC PROPERTIES**).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Systemic adverse drug reactions following the appropriate use of VERSATIS® are unlikely since the systemic concentration of lidocaine is very low (see Section **5.2 PHARMACOKINETIC PROPERTIES**). Systemic adverse drug reactions to lidocaine are similar in nature to those observed with other amide local anaesthetic agents (see Section **4.9 OVERDOSE**).

Adverse events identified in clinical trials

Adverse events occurring in at least 1.5% of patients treated for up to 6 months are displayed in Table 1. The adverse events listed may be associated with the underlying disease and concomitant medications.

Table 1 **Percentage of patients with reported adverse events ≥1.5% (independent from causal relationship) in the safety population of 3 clinical trials**

MedDRA primary system organ class	**Preferred term**	**Patients valid for safety analysis (n = 306)** Percentage of patients with adverse events
Total number of events	-	256
Total percentage of patients with adverse events	-	36.9%
Cardiac disorders	-	3.6%
Eye disorder	-	2.0%
Gastrointestinal disorder	-	4.6%
	Nausea	2.0%
General disorders and administration site conditions	-	11.1%
	Application site burning	1.6%
	Application site erythema	3.6%
	Application site pain	1.6%
	Application site pruritus	2.0%
Infections and infestations		6.9%

MedDRA primary system organ class	Preferred term	Patients valid for safety analysis (n = 306) Percentage of patients with adverse events
	Nasopharyngitis	2.0%
Injury, poisoning, and procedural complications	-	2.9%
Investigations	-	1.6%
Musculoskeletal and connective tissue disorders	-	3.9%
Nervous system disorders	-	6.9%
	Headache	4.9%
Psychiatric disorders	-	1.6%
Respiratory, thoracic, and mediastinal disorders	-	1.6%
Skin and subcutaneous tissue disorders	-	8.2%
	Erythema	3.3%
	Pruritus	2.0%
	Rash	2.3%
Vascular disorders	-	2.0%

Adverse drug reactions identified in clinical trials

Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Approximately 16% of patients can be expected to experience adverse drug reactions. These are localised reactions due to the nature of the medicinal product.

The most commonly reported adverse drug reactions were skin reactions (such as erythema, rash, application site pruritus, application site burning, application site dermatitis, application site erythema, application site vesicles, dermatitis, skin irritation, and pruritus).

Table 2 lists adverse drug reactions that have been reported in studies of post-herpetic neuralgia patients receiving VERSATIS®. They are listed by system organ class and frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 2 Adverse Drug Reactions reported in studies of post herpetic neuralgia patients receiving VERSATIS®

Body system	Frequency	Adverse Drug Reaction
Skin and subcutaneous tissues disorders	Uncommon	Skin lesion
Injury, poisoning and procedural complications	Uncommon	Skin injury
General disorders and administration site conditions	Very common	Administration site reactions

All adverse drug reactions were predominantly of mild and moderate intensity. Of those less than 5% lead to treatment discontinuation.

Post marketing experience

Additionally, Table 3 presents adverse drug reactions have been observed in patients receiving VERSATIS® under post marketing conditions:

Table 3 Adverse Drug Reactions Observed in Patients Receiving VERSATIS® Under Post Marking Conditions

Body system	Frequency	Adverse Drug Reaction
Injury, poisoning and procedural complications	Very rare	Open wound
Immune system disorders	Very rare	Anaphylactic reaction, hypersensitivity

All adverse drug reactions were predominantly of mild and moderate intensity. Of those less than 5% led to treatment discontinuation.

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

Overdose with VERSATIS® is unlikely but it cannot be excluded that inappropriate use, such as use of a higher number of patches at the same time, with prolonged application period, or using VERSATIS® on broken skin might result in higher than normal plasma concentrations. Possible signs of systemic toxicity will be similar in nature to those observed after administration of lidocaine as a local anaesthetic agent and may include the following signs and symptoms: dizziness, vomiting, drowsiness, dysgeusia, seizures, mydriasis, bradycardia, arrhythmia, and shock.

In addition, known drug interactions related to systemic lidocaine concentrations with beta blockers, CYP3A4 inhibitors (e.g. imidazole derivatives, macrolides) and antiarrhythmic agents might become relevant with overdose.

In case of suspected overdose, VERSATIS® should be removed and supportive measures taken as clinically needed. If there is any suspicion of lidocaine overdose, drug blood concentration should be checked. There is no antidote to lidocaine.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: local anaesthetics, amides

Mechanism of action

Lidocaine is a local anaesthetic of the amide type which stabilises excitable membranes by inactivation of sodium channels. Its action on neuronal membranes prevents neuronal conduction. When applied topically in the form of VERSATIS®, lidocaine produces a local analgesic effect.

VERSATIS® has a dual mode of action: the pharmacological action of lidocaine diffusion and the mechanical action of the hydrogel patch that protects the hypersensitive area. The lidocaine contained in VERSATIS® diffuses continuously into the skin, providing a local analgesic effect.

Clinical trials

Pain management in PHN is difficult. There is evidence of efficacy with VERSATIS® in the symptomatic relief from the allodynic component of PHN in some cases.

There were two key controlled studies carried out to assess the efficacy of VERSATIS®. A third study provides information on maintenance of effect.

Efficacy was demonstrated in a multicentre, enriched enrolment, double-blind placebo-controlled, multiple-dose, randomised-withdrawal, parallel-group study with VERSATIS® and corresponding placebo patch. This study had an initial 8-week run-in, open-label phase in which patients with PHN responding to treatment were randomised to a 2-week, double-blind treatment period with either VERSATIS® or placebo patch. PHN was defined as neuropathic pain persisting for at least 3 months after healing of a herpes zoster skin rash.

Patients aged 50 years and older, suffering from PHN and having an average pain intensity (during last week prior to screening and enrolment visit) of at least 4 on the 11-point numeric rating scale (NRS) applied VERSATIS® for up to 8 weeks. Only those patients who reported regular use of VERSATIS® during the last 4 weeks of the run-in phase, an average daily pain intensity of 7 or less on the 11-point NRS in the last week prior to randomisation, increase in pain intensity when VERSATIS® was not worn, and an average pain relief of 'moderate' or better at randomisation (recall period of 1 week prior to the visit) were considered to be responders and were eligible for randomisation.

The primary endpoint was the time-to-exit during the double-blind phase due to lack of efficacy (decrease of pain relief score by two or more categories on a 6-item pain relief scale on two consecutive application days in comparison to the average pain relief in last week on treatment with VERSATIS® before randomisation in run-in phase).

Of the 265 patients, 137 (52%) entered the run-in phase and responded to VERSATIS®. Of these, 71 were randomised to the double-blind phase. About 40% of patients randomised to each treatment group were not regularly taking any concomitant medication for PHN pain at study entry. The median time-to-exit the double-blind period was 13.5 days for patients randomised to VERSATIS® (n = 36) and 9.0 days for those randomised to placebo patch (n = 35). This difference was not statistically significant. For the per-protocol population, median time-to-exit was 14 days for VERSATIS® (n = 17) and 6 days for the placebo patch (n = 17). This difference between groups was statistically significant.

Post hoc analyses of this study showed that the initial response was independent of the duration of pre-existing PHN. However, the notion that patients with longer duration of PHN (>12 months) do benefit more from active treatment is supported by the finding that this group of patients was more likely to drop out due to lack of efficacy when switched to placebo during the double-blind withdrawal part of this study.

A double-blind, placebo-controlled, cross-over trial was conducted to test whether patients who had been using VERSATIS® could distinguish between the lidocaine patch and a placebo patch. Half of the patients were randomised to receive VERSATIS® as first treatment and half received the placebo patch as first treatment then vice versa in the second treatment phase. After up to 14 days in the first phase patients were directly switched to second treatment phase. The primary endpoint was 'time to exit' comparing treatment phases.

Patients were to withdraw from the treatment phase if their pain relief was 2 points lower than their usual response to VERSATIS® on a 6-point verbal rating scale (worse, no pain relief, slight relief, moderate relief, a lot of relief, complete relief). The secondary end point was patient's preference between treatments. Of the 33 patients with PHN in this study, 32 of them received the investigational products and completed the study. In general, patients used up to 3 patches per application with only three exceptions (two patients used up to 4 and one patient 5 patches per application). The median times to exit in each treatment arm were >14 days for VERSATIS® and 3.8 days for placebo patch (across both treatment periods), $p<0.001$. Three patients (9.4%) preferred placebo patch, 25 patients (78.1%) preferred VERSATIS®, and 4 patients (12.5%) had no preference.

Maintenance of efficacy was assessed over up to 12 months in an open-label, multicentre, multiple-dose study conducted in 259 patients aged 50 years and older with PHN for >3 m after herpes zoster (HZ) rash healing who participated in an earlier efficacy study, or had PHN with average pain intensity of ≥ 4 (0–11 scale) over last week prior to screening. At 12 months, 143 patients had completed the study. Pain relief was generally maintained.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The amount of lidocaine systemically absorbed from VERSATIS® is directly related to both the duration of application and the surface area over which it is applied. When VERSATIS® is used according to the maximum recommended dose (3 patches applied simultaneously for 12 h) about 3±2% of the total applied lidocaine dose is systemically available and similar for

single and multiple administrations. Maximum systemic concentrations of lidocaine were observed between 9 and 12 h after application of VERSATIS®.

A population kinetics analysis of the clinical efficacy studies in patients suffering from post-herpetic neuralgia (PHN) revealed a mean maximum concentration for lidocaine of 45 ng/mL after application of 3 patches simultaneously 12 h per day after repeated application for up to one year. This concentration is in accordance with the observation in pharmacokinetic studies in PHN patients (52 ng/mL) and in healthy volunteers (85 ng/mL and 125 ng/mL).

For lidocaine and its metabolites MEGX, GX, and 2,6 xylidine no tendency for accumulation was found; steady state concentrations were reached within the first four days.

The population kinetic analysis indicated that when increasing the number from 1 to 3 patches worn simultaneously, the systemic exposure increased less than proportionally to the number of used patches.

Distribution

After intravenous administration of lidocaine to healthy volunteers, the volume of distribution was found to be 1.3 ± 0.4 L/kg (mean ± S.D., n = 15). The lidocaine distribution volume showed no age dependency; however, it is decreased in patients with congestive heart failure and increased in patients with liver disease. At plasma concentrations produced by application of VERSATIS®, approximately 70% of lidocaine is bound to plasma proteins. Lidocaine crosses the placental and blood-brain barriers presumably by passive diffusion.

Metabolism

Lidocaine is metabolised rapidly in the liver to a number of metabolites. The primary metabolic route for lidocaine is N-dealkylation to monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which are less active than lidocaine and available in low concentrations. These are hydrolysed to 2,6-xylidine, which is converted to 4-hydroxy-2,6-xylidine and the N-hydroxylation product N-(2,6-dimethlyphenyl)hydroxylamine (DMHA).

The metabolite, 2,6-xylidine, has unknown pharmacological activity but has shown carcinogenic potential in rats (see Section **5.3 PRECLINICAL SAFETY DATA**). A population kinetics analysis revealed a mean maximum concentration for 2,6-xylidine of 9 ng/mL after repeated daily applications for up to one year. This finding is confirmed by a phase I pharmacokinetic study.

Lidocaine may undergo metabolism in the skin.

Excretion

Lidocaine and its metabolites are excreted by the kidneys. More than 85% of the dose is found in the urine in the form of metabolites or active substance. Less than 10% of the lidocaine dose is excreted unchanged. The main metabolite in urine is a conjugate of 4-hydroxy-2,6-xylidine, accounting for about 70 to 80% of the dose excreted in the urine. 2,6-xylidine is excreted in the urine in man at a concentration of less than 1% of the dose. The elimination half-life of lidocaine after patch application in healthy volunteers is 7.6 hours. After multiple administration of VERSATIS® in healthy subjects, the elimination half-lives of MEGX, GX and 2,6-xylidine are 6.4 h, 13 h, and 15 h respectively. The systemic clearance of lidocaine is 0.635 ± 0.175 L/min.

The excretion of lidocaine and its metabolites may be delayed in cardiac, renal or hepatic insufficiency.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lidocaine itself has shown no evidence of genotoxicity when investigated *in vitro* or *in vivo*. Metabolites of lidocaine, 2,6-xylidine and N-(2,6-dimethylphenyl)- hydroxylamine (DMHA), have shown genotoxic activity in several assays.

Carcinogenicity

Carcinogenicity studies have not been performed with lidocaine. A two-year dietary study in rats with the metabolite 2,6-xylidine noted inflammation and hyperplasia of the nasal olfactory epithelium and carcinomas and adenomas in the nasal cavity.

Tumorigenic changes were also found in the liver and subcutis. Estimated 2,6-xylidine exposure (plasma AUC) at the lowest tumorigenic dose was at least 60-fold clinical exposure at the maximum recommended human dose (MRHD) of VERSATIS® dermal patch. Because the risk to humans is unclear, long term treatment with high doses of lidocaine should be avoided.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Self-adhesive layer: glycerol, sorbitol solution (70%) (crystallising), carmellose sodium, propylene glycol, urea, heavy kaolin, tartaric acid, gelatin, polyvinyl alcohol, aluminium glycinate, disodium edetate, methyl hydroxybenzoate, propyl hydroxybenzoate, polyacrylic acid, sodium polyacrylate, purified water.

Backing fabric and release liner: Polyethylene terephthalate (PET).

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

Store below 25°C. Do not refrigerate or freeze.

After first opening: keep the sachet tightly closed.

Use opened sachets within 14 days.

6.5 NATURE AND CONTENTS OF CONTAINER

VERSATIS® dermal patches are contained in a resealable sachet composed of paper/ polyethylene/aluminium/ethylene meta-acrylic acid co-polymer containing 5 patches.

Each carton contains 5, 10, 20, 25 or 30 patches. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

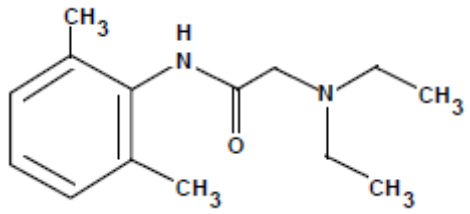
After use VERSATIS® still contains active substance. After removal, the used patches should be folded in half, adhesive side inwards, so that the self-adhesive layer is not exposed, and the patch should be discarded.

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Structural Formula:



Chemical Name: 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide

Molecular Formula: $C_{14}H_{22}N_2O$

Molecular Weight: 234.3

CAS number

137–58–6

Lidocaine is a white or almost white crystalline powder, practically insoluble in water, very soluble in ethanol, and freely soluble in ether. The pKa is 7.9. The coefficient (log D) is defined as the ratio of the equilibrium concentrations of a single molecular species in a 1 octanol/aqueous buffered solution 2 phase system at pH 7.4. The value of log D for lidocaine in 1 octanol/water is 1.61.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Seqirus Pty Ltd
ABN 26 160 735 035
63 Poplar Road
Parkville, VIC 3052
Australia
Telephone: 1800 642 865
www.seqirus.com.au

9 DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods

16 March 2012

AUST R 175178

10 DATE OF REVISION

04 January 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted to align with the Form for providing the Product Information March 2018. Minor editorial changes as well as changing the API name as per AAN.