

**Attachment 1: Product information for AusPAR - ACTAIR initiation treatment 100 IR and 300 IR and continuation treatment 300 IR - American House Dust Mite / European House Dust Mite allergen extracts - Stallergenes Australia Pty Ltd - PM-2014-03871-1-2 - FINAL 9 August 2017. This Product Information was approved at the time this AusPAR was published.**

Product Information:

ACTAIR 100 IR and 300 IR sublingual tablets

Final 1.0

# PRODUCT INFORMATION

## NAME OF MEDICINE

### ACTAIR Initiation Treatment Sublingual Tablets 100 IR & 300 IR

**Mixture of American (*D. farinae*) and European (*D. pteronyssinus*) House dust mite allergen extracts**

### ACTAIR Continuation Treatment Sublingual Tablets 300 IR

**Mixture of American (*D. farinae*) and European (*D. pteronyssinus*) House dust mite allergen extracts**

## DESCRIPTION

A 50% mixture of House dust mite allergen extracts from: European house dust mites (*Dermatophagoides pteronyssinus*) and American house dust mites (*Dermatophagoides farinae*), 100 IR\* or 300 IR\* per sublingual tablet.

\* IR (Index of Reactivity): The IR unit has been defined to measure the allergenicity of an allergen extract. The allergen extract contains 100 IR/mL when, on a skin prick-test using a Stallerpoint®, it induces a wheal diameter of 7 mm in 30 patients sensitized to this allergen, (geometric mean). The cutaneous reactivity of these patients is simultaneously demonstrated by a positive skin prick-test to either 9% codeine phosphate or 10 mg/mL histamine. The IR unit of Stallergenes is not comparable to the units used by other allergen manufacturers.

**Excipients:** Mannitol, Microcrystalline cellulose, Croscarmellose sodium, Colloidal anhydrous silica, Magnesium stearate and Lactose monohydrate.

One sublingual tablet of 100 IR contains 82.8 – 83.3 mg Lactose monohydrate.

One sublingual tablet of 300 IR contains 80.8 – 82.3 mg Lactose monohydrate.

## PHARMACOLOGY

Pharmacotherapeutic group: Allergen extract, house dust mites

ATC code: V01AA03

### ***Mechanism of action***

Immunologic changes associated with immunotherapy are complex, and the exact mechanism(s) responsible for its clinical efficacy are unknown.

The allergic reaction is dependent on the presence of allergen-specific Immunoglobulin E (IgE) antibodies bound to specific receptors on mast cells and basophils. Upon interaction of allergens with such cell-bound IgE antibodies, histamine and other mediators are released and produce local or systemic responses in atopic individuals.

The immunologic response to allergen immunotherapy is characterized by changes in allergen specific antibody responses (with a decrease in IgE and the induction of IgG<sub>4</sub> antibodies) as well as in the polarization of CD4+ T-cell responses (from a Th2 to a regulatory T-cell pattern).

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### ***Pharmacodynamic properties***

Treatment with ACTAIR has been shown to induce a systemic antibody response towards house dust mite allergens, with an increase in specific IgG<sub>4</sub> antibodies in some patients. These immunoglobulins may compete with IgE for allergen binding, thereby decreasing allergen capture and presentation.

### ***Pharmacokinetic properties***

Allergens in ACTAIR consist mainly of proteins and glycoproteins. There is no direct bioavailability of intact allergens in the blood. Therefore, no pharmacokinetic studies in animals or in humans have been carried out to investigate the pharmacokinetic profile and metabolism of ACTAIR.

## **CLINICAL TRIALS**

### ***Clinical experience in adults: Study 1***

During a European, multicenter, multinational, randomized, double-blind, placebo-controlled study conducted over 2 years, 509 patients received either the 300 IR dose (n=170) or the 500 IR dose (n=169) sublingual tablet of house dust mites allergen extract or placebo (n=170) daily for 12 months and were followed up during the subsequent treatment-free year.

Study patients had allergic rhinitis caused by house dust mites, confirmed by positive skin tests and *in vitro* testing for dust mites-specific IgE antibodies. Patients with intermittent asthma were included. Approximately 30% had asthma at baseline and 52% were poly-sensitized (i.e., sensitized to house dust mites allergens and at least one of the other allergens tested).

Efficacy was assessed via daily recording of rhinitis symptoms and rescue medication use by patients.

Patients receiving the 300 IR dose had a lower Average Adjusted Symptom Score over the last 3 months of treatment by 17.9% than those receiving placebo.

The results of the primary efficacy analysis are presented in the table below:

Table 1 Average Adjusted Symptom Score<sup>1</sup>

Dosage	N	Average Adjusted Symptom Score	Difference from placebo	p-value	Relative difference from placebo
300 IR	141	3.18	-0.69	0.0150	-17.9%
Placebo	153	3.87	—	—	—

N = number of subjects with data

<sup>1</sup>The Average Adjusted Symptom Score adjusts the symptom score (the sum of sneezing, rhinorrhoea, nasal pruritus and nasal congestion scores, using a score from 0 to 3) for rescue medication use (i.e., antihistamines and corticosteroids). It ranges from 0 to 12.

Patients receiving the 300 IR dose had a lower Average Rhinitis Total Symptom Score by 18.5% than those receiving placebo. There was no difference in the Average Rescue Medication Score between the active and placebo treatment groups.

The individual symptom scores for sneezing, nasal pruritus and nasal congestion were significantly reduced in the 300 IR group by 19.0%, 21.2%, and 20.7%, respectively, compared to the placebo group. *The reductions observed for rhinorrhoea (12.2%) and ocular itching (20.5 %) were not statistically significant”.*

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A significant overall improvement of 23.0% was demonstrated in the Rhinoconjunctivitis Quality of Life Questionnaire score in the 300 IR group versus the placebo group in the first year. The improvement was also observed for each of the 7 domains: activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional.

At the end of treatment, the proportion of patients reporting marked improvement was higher in the 300 IR group (36.9%) than in the placebo group (18.0%) with significantly higher treatment success (80.5% for 300 IR and 59.6% for placebo).

### ***Clinical experience in adults and adolescents (12-17): Study 2***

During a multicenter, randomized, double-blind, placebo-controlled study conducted in Japan over one treatment year, 968 adults and adolescents aged 12 to 64 years received either a 300 IR dose (n=322) or a 500 IR dose (n=324) of sublingual tablet of house dust mites allergen extract or placebo (n=322) daily for 12 months.

Study patients had allergic rhinitis caused by house dust mites, confirmed by positive nasal provocation test and *in vitro* testing for dust mites-specific IgE antibodies. Patients with intermittent or mild asthma were included.

Patients receiving the 300 IR dose had a lower Average Adjusted Symptom Score over the last 2 months of treatment by 18.2% than those receiving placebo.

The results of the primary efficacy analysis are presented in the table below:

Table 2 Average Adjusted Symptom Score<sup>1</sup>

Dosage	N	Average Adjusted Symptom Score	Difference from placebo	p-value	Relative difference from placebo
300 IR	315	5.00	-1.11	<0.0001	-18.2%
Placebo	316	6.11	—	—	—

N = number of subjects with data

<sup>1</sup>The Average Adjusted Symptom Score adjusts the symptom score (the sum of sneezing, rhinorrhoea and nasal congestion scores, using a score from 0 to 4, and nasal pruritus using a score from 0 to 3) for rescue medication use (i.e., antihistamines and corticosteroids). It ranges from 0 to 15.

In the subset of adolescents (aged 12 to 17 years), patients receiving the 300 IR dose had a lower Average Adjusted Symptom Score by 26.9% than those receiving placebo.

Patients receiving the 300 IR dose had a lower Average Rhinitis Total Symptom Score by 17.7% and a lower Average Rescue Medication Score by 41.6% than those receiving placebo.

The individual symptoms scores for sneezing, rhinorrhoea, nasal pruritus, nasal congestion and eye tearing were significantly reduced in the 300 IR group by 11.4%, 17.8%, 17.7%, 22.8% and 18.1%, respectively, compared to the placebo group.

For each of the domains of the Japanese Rhinoconjunctivitis Quality of Life Questionnaire score (i.e., "Nasal and Eye symptoms," "QOL-related Questionnaire" and "General State"), a significant improvement was demonstrated at the end of the treatment in patients receiving 300 IR compared to those receiving placebo.

At the end of treatment, the proportion of patients reporting marked improvement was higher in the 300 IR group (22.2%) than in the placebo group (9.7%).

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***Clinical experience in children: Study 3*** During a European, multinational, randomized, double-blind, placebo-controlled study, 471 patients from 5 to 17 years old received either the 300 IR dose (n=241) of sublingual tablet of house dust mites allergen extract or placebo (n=230) daily for 12 months. The patients were not sufficiently symptomatic to enable assessment of the efficacy of ACTAIR.

## **INDICATIONS**

Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults and adolescents over 12 years diagnosed with house dust mite allergy.

## **CONTRAINDICATIONS**

- Hypersensitivity to any of the excipients;
- Severe, uncontrolled or unstable asthma;
- Immune deficiency diseases or active forms of auto-immune disorder
- Malignant diseases (e.g., cancer);
- Oral inflammations (such as oral lichen planus, oral ulcerations or oral mycosis).

## **PRECAUTIONS**

In case of oral surgery, including dental extraction, treatment with ACTAIR should be stopped until complete healing.

In general, if treatment is interrupted for less than 7 days, it is to be continued. Should the interruption period be longer than 7 days, it is recommended to continue treatment only after seeking medical advice.

For the treatment of allergic rhinitis, ACTAIR has been evaluated in patients with or without asthma requiring therapies consistent with GINA treatment step 1. In ongoing clinical studies conducted to evaluate the efficacy and safety of the treatment for asthma, no safety findings have been detected with doses up to 1500 IR in patients with asthma controlled or partly controlled by therapies consistent with GINA treatment step 2, 3 or 4.

Severe allergic reactions may be treated with adrenaline. The effects of adrenaline may be potentiated in patients treated with tricyclic antidepressants and mono amine oxidase inhibitors (MAOIs) with possible fatal consequences; this should be taken into consideration prior to initiating specific immunotherapy.

Clinical experience in relation to simultaneous vaccination and treatment with ACTAIR is missing. Vaccination may be given without interrupting treatment with ACTAIR after medical evaluation of the general condition of the patient.

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

Eosinophilic esophagitis has been reported in association with sublingual immunotherapy. During treatment with ACTAIR, if severe or persistent gastrointestinal symptoms including dysphagia or chest

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pain occur, ACTAIR should be interrupted and the patient evaluated by their physician. Treatment should only be resumed upon instruction of the physician. Patients with a history of eosinophilic esophagitis should be warned of the association of sublingual immunotherapy and eosinophilic esophagitis

Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of adrenaline used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiotonically and bronchodilating effects of adrenaline

### ***Carcinogenicity***

Carcinogenicity studies have not been conducted with ACTAIR.

### ***Genotoxicity***

ACTAIR active substances revealed no evidence of mutagenic or clastogenic potential based on the results of *in vitro* genotoxicity tests (bacterial reverse mutation, mouse lymphoma thymidine kinase and micronucleus assays).

### ***Effects on fertility***

There are no fertility data available in humans.

Animal fertility studies have not been conducted with ACTAIR active substances. However, histopathological examination of the male and female reproductive organs revealed no adverse effects in the repeat-dose toxicity studies with mite allergen extracts.

### ***Interaction with other medicinal products***

No interactions were reported in clinical trials with ACTAIR, during which patients were able to take medications to treat allergic symptoms (antihistamines, corticosteroids).

There are no data on possible risks of simultaneous immunotherapy with other allergens during treatment with ACTAIR.

### ***Use in Pregnancy (Category B2)***

There are no adequate and well-controlled studies of ACTAIR in pregnant women.

There was no evidence of maternal and embryofetal development toxicity following oral administration of ACTAIR active substances to pregnant rats and rabbits, commencing on gestation day 6, at doses at least 76 times the 300 IR ACTAIR dose, based on body surface area. No peri-postnatal toxicity study has been conducted.

As a precautionary measure, it is preferable to avoid initiating treatment during pregnancy.

If pregnancy occurs during treatment, the treatment may be continued with close medical supervision.

### ***Use in Lactation***

No clinical data are available for the use of ACTAIR during lactation. Studies in animals to investigate excretion of ACTAIR into milk were not conducted.

No effects on the breastfed infants are anticipated. It is not recommended to initiate immunotherapy during breast-feeding. However, if a patient is under treatment at delivery, she can breast-feed with close supervision.

### ***Use in Children (<5 years)***

Clinical experience with ACTAIR in children <5 years is not available.

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

ACTAIR has no known influence on the ability to drive and use machines.

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## ADVERSE EFFECTS

During treatment with ACTAIR, patients are exposed to allergens that may cause application site reactions and/or systemic allergic symptoms. Application site reactions (e.g., oral pruritus and mouth oedema) of mild or moderate severity may therefore be expected during the period of therapy.

As with any allergen immunotherapy, severe allergic reactions including severe laryngopharyngeal disorder or systemic allergic reactions (i.e., acute onset of an illness with involvement of the skin, mucosal tissue, or both, respiratory compromise, persistent gastrointestinal symptoms, or reduced blood pressure and/or associated symptoms) can rarely occur. Patients should be informed of the associated signs and symptoms. Should these occur, patients should discontinue therapy and seek immediate medical care and treatment should only be resumed at the instruction of a physician.

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

### ***Adults and adolescents***

In study 1, 339 adults with house dust mites-associated allergic rhinitis with or without intermittent asthma were treated daily with the 300 IR dose (n=170) or the 500 IR dose (n=169).

A total of 221 patients (65.2%) receiving the active treatment (111 in the 300 IR group and 110 in the 500 IR group) reported adverse reactions as did 38 (22.4%) of those receiving placebo.

In study 2, 646 adults and adolescents (aged 12 to 64 years) with house dust mites-associated allergic rhinitis with or without intermittent or mild asthma were treated with the 300 IR dose (n=322) or the 500 IR dose (n=324).

A total of 452 patients (70.0%) receiving the active treatment (215 in the 300 IR group and 237 in the 500 IR group) reported adverse reactions as did 60 (18.6%) of those receiving placebo.

In both studies, most adverse reactions leading to premature study withdrawal were application site reactions, were of mild or moderate severity and were non-serious.

Adverse events reported at an incidence of  $\geq 2\%$  of patients receiving ACTAIR 300 IR in Study 1 and Study 2 pooled data are listed in Table 3.

Table 3 Adverse Events Reported by  $\geq 2\%$  of Patients Receiving ACTAIR 300 IR

System Organ Class Preferred Term	ACTAIR 300 IR (N=492)	Placebo (N=492)
<b>Ear and labyrinth disorders</b>		
Ear pruritus	10.0%	0.8%
<b>Gastrointestinal disorders</b>		
Oedema mouth	17.9%	0.4%
Oral pruritus	17.7%	3.0%
Stomatitis	7.5%	4.1%
Abdominal pain	5.1%	2.8%
Tongue oedema	4.7%	0.2%
Lip oedema	3.7%	0.0%
Oral discomfort	3.5%	1.2%
Diarrhoea	3.0%	1.6%
Nausea	3.0%	1.4%

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System Organ Class	ACTAIR 300 IR (N=492)	Placebo (N=492)
Preferred Term		
Paraesthesia oral	2.4%	0.8%
Dyspepsia	2.0%	0.8%
<b>System Organ Class</b>	<b>ACTAIR 300 IR (N=492)</b>	<b>Placebo (N=492)</b>
<b>Respiratory, thoracic and mediastinal disorders</b>		
Throat irritation	22.2%	3.9%
Oropharyngeal discomfort	3.7%	0.8%
Cough	3.3%	4.5%
Pharyngeal oedema	3.3%	0.2%
Dyspnoea	2.2%	1.2%
<b>Infections and infestations</b>		
Nasopharyngitis	29.5%	31.5%
Gastroenteritis	5.1%	4.7%
Bronchitis	4.3%	2.6%
Acute tonsillitis	2.6%	1.6%
<b>Nervous system disorders</b>		
Headache	6.5%	7.5%
<b>Skin and subcutaneous tissue disorders</b>		
Dermatitis atopic	5.1%	5.9%

Adverse events with an incidence <2% and with causality assigned to ACTAIR are listed below according to the MedDRA convention by system organ class and by frequency into common: ≥1/100, <1/10, uncommon: ≥1/1,000, <1/100, rare: ≥1/10,000, <1/1,000.

### **Ear and labyrinth disorders**

Common: Ear pain

### **Gastrointestinal disorders**

Common: Glossitis, oral mucosal blistering, hypoesthesia oral, gastritis, cheilitis

Uncommon: Oral pain, tongue pruritus, dysphagia, glossodynia, vomiting, gingivitis, gastrointestinal disorder, palatal oedema, dry mouth, lip pruritus, breath odour, chapped lips, frequent bowel movements, irritable bowel syndrome, gingival pain, mouth ulceration, odynophagia, oesophageal discomfort, salivary gland enlargement, salivary hypersecretion

### **Respiratory, thoracic and mediastinal disorders**

Common: Dry throat

Uncommon: Laryngeal oedema, wheezing, asthma, oropharyngeal pain, pharyngolaryngeal pain, sneezing, rhinorrhoea, nasal discomfort, nasal congestion, throat tightness

### **Cardiac disorders**

Uncommon: Tachycardia

### **Eye disorders**

Common: Conjunctivitis

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Uncommon: Eye oedema, blepharospasm, lacrimation increased

### **General disorders and administration site conditions**

Uncommon: Chest discomfort, lump feeling in throat, chest pain, asthenia, malaise

### **Infections and infestations**

Uncommon: Periodontitis

### **Musculoskeletal and connective tissue disorders**

Uncommon: Muscle spasms

### **Nervous system disorders**

Uncommon: Somnolence

### **Psychiatric disorders**

Uncommon: Anxiety

### **Skin and subcutaneous tissue disorders**

Common: Pruritus, urticaria

Uncommon: Rash, angioedema, blister

### **Investigations**

Common: Gamma glutamyltransferase increased

Uncommon: Alanine aminotransferase increased, lymphocyte morphology abnormal, aspartate aminotransferase increased, basophil count increased, blood bilirubin increased, blood uric acid increased

In addition to the reactions listed in the Tabulated Summary, in a double-blind, placebo-controlled study conducted in an environmental exposure chamber over 6 months, 59 patients with or without intermittent asthma who received ACTAIR 300 IR have reported at least one of the following reactions:

Lip blister, bronchospasm, sinus congestion, rhinitis allergic, ear discomfort, eye pruritus, ocular hyperaemia, paraesthesia, pharyngitis (all reported as common).

### ***Paediatric population (Age 5 to 17)***

In a multicenter, multinational, randomized, double-blind, placebo-controlled paediatric clinical trial, 239 children and adolescents with house dust mites-associated allergic rhinitis were treated with ACTAIR 300 IR once daily over 12 months.

Overall, the safety profile in the paediatric population was similar to that of adults. In addition to the reactions listed in the Tabulated Summary, the following reactions were reported:

Enterocolitis, oral disorder, seborrhoea, bronchitis, candida infections, and ear disorder (all reported as uncommon) and malaise (reported at a higher frequency than in adults i.e. common).

### **Potential adverse effects experienced with the same class of product**

Cases of eosinophilic esophagitis have been reported with other sublingual immunotherapy products.

## **DOSAGE AND ADMINISTRATION**

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Treatment with ACTAIR should only be prescribed and initiated by physicians with adequate training and experience in the treatment of allergic diseases. In the case of treatment of adolescent patients over 12 years, the physicians should have the corresponding training and experience in patients in this age group.

It is recommended that the first tablet of ACTAIR is taken under medical supervision and that the patient is monitored for 30 minutes.

*Method of administration*

On the first day, one 100 IR tablet should be taken. Tablets must be placed under the tongue until complete disintegration and then swallowed. On the second day of treatment, two 100 IR tablets must be placed under the tongue simultaneously and then swallowed.

It is recommended that the tablets be taken during the day in an empty mouth.

*Dose regimen in adults and adolescents over 12 years.*

The therapy is composed of an initiation treatment (including a 3-day dose escalation) and a continuation treatment.

The initiation treatment pack corresponds to the first month of treatment with ACTAIR 100 IR & 300 IR sublingual tablets:

<b>Small blister</b>	Day 1	1 x 100 IR tablet
	Day 2	2 x 100 IR tablets
	Day 3	1 x 300 IR tablet
	Day 4	1 x 300 IR tablet
	Day 5	1 x 300 IR tablet
	.	
	.	
<b>Large blister</b>	Day 30	1 x 300 IR tablet

From the 2<sup>nd</sup> month onwards, treatment must be continued with the continuation treatment packs, with one ACTAIR 300 IR sublingual tablet per day until the end of treatment.

Study 1 has shown that, after one year of treatment in adults, efficacy is demonstrated during the subsequent treatment free year.

*Duration of treatment*

Efficacy has been demonstrated for one year of treatment with additional clinical data available for one year post-treatment.

*Special Population:*

Clinical experience on immunotherapy with ACTAIR in patients older than 65 years is lacking.

*Paediatric population*

The safety and efficacy of ACTAIR in children below the age of 5 years is lacking.

## **OVERDOSAGE**

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Overdoses of up to 1000 IR for up to 28 days were reported in patients receiving ACTAIR. Higher doses may be associated with reduced tolerability and may potentially increase the risk of serious allergic reactions.

In the event of an overdose, the adverse effects should be treated symptomatically.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

## **PRESENTATION AND STORAGE CONDITIONS**

ACTAIR is presented as white to beige, brown speckled tablet. The 100 IR tablets are engraved "SAC" on one side and "100" on the other and the 300 IR tablets are engraved "SAC" on one side and "300" on the other.

### Initiation treatment

Pack of 1 x 3 sublingual tablets of 100 IR in a small blister + 1 x 28 sublingual tablets of 300 IR in a blister, pack of 1 x 3 sublingual tablets of 100 IR in a small blister + 88 sublingual tablets of 300 IR in 3 blisters (1 x 28, 1 x 30 and 1 x 30 sublingual tablets) and pack of 1 x 3 sublingual tablets of 100 IR in a small blister + 1 x 7 sublingual tablets of 300 IR in a blister.

### Continuation treatment

1 x 30 sublingual tablets of 300 IR in a blister. Pack of 30 or 90 tablets.

Not all pack sizes may be marketed.

**ACTAIR Initiation Treatment Sublingual Tablets 100 IR & 300 IR (A 50% mixture of Allergen house dust mite extracts of European house dust mite (*D. pteronyssinus*) and American house dust mite (*D. farinae*) - (AUST R233470)**

**ACTAIR Continuation Treatment Sublingual Tablets 300 IR (A 50% mixture of Allergen house dust mite extracts of European house dust mite (*D. pteronyssinus*) and American house dust mite (*D. farinae*) - (AUST R 233471)**

## **STORAGE**

Store below 30°C.

Store in the original package in order to protect from moisture.

## **NAME AND ADDRESS OF THE SPONSOR**

Stallergenes Australia Pty Ltd  
Suite 2408,  
4 Daydream Street,  
Warriewood,  
New South Wales 2102

Ph: 1800 824 166

## **Distributed in Australia by:**

EBOS Group Pty Ltd

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Unit 2A Clayton Business Park

1508 Centre Rd., Clayton

Victoria 3168

## **POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE – S4

## **DATE OF FIRST INCLUSION IN THE ARTG**

TGA approval: 15 April 2016

## **DATE OF MOST RECENT AMENDMENT**