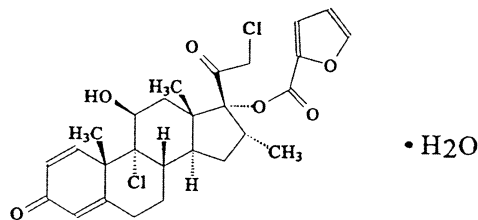


PRODUCT INFORMATION
NASONEX[®] AQUEOUS NASAL SPRAY 0.05%
ALCOHOL FREE

NAME OF THE MEDICINE

NASONEX Aqueous Nasal Spray 0.05% is a metered-dose, manual pump spray unit containing a suspension of mometasone furoate. Each actuation delivers approximately 100 µg of mometasone furoate monohydrate suspension, containing mometasone furoate monohydrate equivalent to mometasone furoate 50 µg.

Chemical structure:



Mometasone furoate monohydrate is 9,21-Dichloro-11 β ,17-dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-(2-furoate) monohydrate. The empirical formula is $\text{C}_{27}\text{H}_{30}\text{Cl}_2\text{O}_6 \cdot \text{H}_2\text{O}$. MW=539.45. CAS Registry number: 83919-23-7 (mometasone furoate anhydrous)

DESCRIPTION

Mometasone furoate is a white to off white powder and it is practically insoluble in water; slightly soluble in menthanol, ethanol and isopropanol; soluble in acetone. NASONEX Aqueous Nasal Spray 0.05% contains mometasone furoate 0.5 mg/g (as the monohydrate).

List of excipients

Dispersible cellulose, glycerol, citric acid monohydrate or anhydrous citric acid, sodium citrate, polysorbate 80 and purified water with benzalkonium chloride 0.2 mg/g as preservative. NASONEX Aqueous Nasal Spray 0.05% does not contain fluorocarbon propellants.

PHARMACOLOGY

Pharmacology and pharmacological actions

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active.

In studies utilising nasal antigen challenge, NASONEX Aqueous Nasal Spray 0.05% has shown anti-inflammatory activity in both the early- and late-phase allergic responses. This has been demonstrated by decreases (vs placebo) in histamine and eosinophil activity and reductions (vs baseline) in eosinophils, neutrophils and epithelial cell adhesion proteins.

Pharmacokinetics

Systemic bioavailability of mometasone furoate was investigated in 24 healthy volunteers following intranasal administration of 400 µg of the suspension. Mometasone was detectable in plasma (at sporadic time points) in only 4 of the 24 subjects, despite the use of a sensitive assay with a limit of quantitation of 50 pg/mL. Thus, there were no relevant pharmacokinetic data for this dosage form.

Systemic absorption of mometasone furoate suspension administered as aqueous nasal spray, 200µg single dose, was measured using a sensitive assay with a lower quantitation limit of 0.25 pg/mL. Mean C max was 5.77 pg/mL (CV% 32) and mean AUC (0-12hr) 29.6pg.hr/mL (CV% 37). When compared with dose adjusted PK data for IV mometasone administration from earlier studies with a quantitation limit of 50 pg/mL and longer sampling duration, the estimated relative systemic (or 'absolute') bioavailability is < 1%. The bioavailability of mometasone following intranasal administration is low

Systemic effects were not detected in adults, adolescents or children following the administration of mometasone furoate aqueous nasal spray.

Mometasone furoate suspension is very poorly absorbed from the gastrointestinal tract, and the small amount that may be swallowed and absorbed undergoes extensive first-pass metabolism prior to excretion in urine and bile.

CLINICAL TRIALS

ADULT CLINICAL PROGRAM

Allergic Rhinitis: The clinical program evaluated the efficacy and safety of NASONEX Aqueous Nasal Spray 0.05% in the prophylaxis and treatment of seasonal allergic rhinitis and the treatment of perennial allergic rhinitis. Five Phase I clinical studies evaluated the systemic safety and local tolerability of NASONEX. Other clinical studies included:

- One Phase II dose-ranging study conducted to determine the optimum dose for the Phase III program;
- Seven Phase III studies designed to assess the safety and efficacy of NASONEX in treating seasonal allergic rhinitis for 28 days (including two studies which evaluated the prophylactic efficacy of NASONEX in preventing the symptoms of seasonal allergic rhinitis, and two which evaluated inflammatory response markers following nasal provocation with allergens); and
- Five Phase III studies designed to assess the safety and efficacy of NASONEX in the treatment of perennial allergic rhinitis for 12 weeks. Four studies investigated the long term safety and maintenance of therapeutic effect of NASONEX over 52 weeks; one perennial allergic rhinitis study was conducted in the elderly population; and three open-label perennial allergic rhinitis studies included a "variable-dose group" in which the dose of NASONEX varied from 100 to 400µg daily depending on symptoms.

During the course of the Phase II/III clinical program, 3120 patients (12 years of age and older) were treated with NASONEX Aqueous Nasal Spray 0.05%. The majority (65%) of patients was treated with 200 µg once daily. The remainder received NASONEX in a dose ranging from 50 µg to 800 µg once daily. A total of 712 patients were treated with NASONEX for at least 6 months and 350 patients were treated for 12 months or longer.

The results of the efficacy studies demonstrated that NASONEX Aqueous Nasal Spray 0.05% 200 µg/day was consistently superior to placebo in relieving the symptoms of both seasonal allergic rhinitis and perennial allergic rhinitis and was of comparable efficacy to other commonly used topical corticosteroid sprays. In the case of seasonal allergic rhinitis it is also superior to placebo in the prophylaxis of symptoms. In the long-term studies in perennial allergic rhinitis there was no evidence of any diminution of its efficacy over time.

After the first dose of NASONEX, clinically significant improvement of symptoms was achieved within 12 hours in 28% of a group of patients (n=190) with seasonal allergic rhinitis (median = 36 hours). However, the full benefit of treatment may not be achieved in the first 48 hours, therefore, the patient should continue regular use to achieve full therapeutic benefit.

Nasal Polyps: Three studies were conducted to assess the safety and efficacy of NASONEX Aqueous Nasal Spray 0.05% in the treatment of nasal polyps for four months. These included two pivotal trials evaluating doses of 200 µg once or twice daily and a supportive trial evaluating a dose of 200 µg once daily. A total of 594 adult patients (ages 18 to 86 years) received NASONEX Aqueous Nasal Spray 0.05%. The co-primary efficacy endpoints in the pivotal trials were 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of treatment as assessed by endoscopy. Efficacy was demonstrated in both studies at a dose of 200 µg twice daily and in one study at a dose of 200 µg once a day. Improvement in other symptoms of nasal polyps (loss of smell, rhinorrhea and postnasal drip) was also observed after a 1-month treatment with the 200 µg, twice-daily dose compared to placebo in both studies and in one study after once-daily treatment. In the supportive study, patients demonstrated a statistically significant improvement with NASONEX Aqueous Nasal Spray 0.05% at a dose of 200 µg once a day in relief of nasal congestion and reduction of polyp size with 4 months of treatment compared to placebo.

Acute Rhinosinusitis: In two trials with 1954 patients 12 years of age and older with signs and symptoms of acute rhinosinusitis for 7 to 28 days prior to baseline, NASONEX Aqueous Nasal Spray 0.05% 200 µg twice daily was effective in significantly improving symptoms of rhinosinusitis compared to placebo as evaluated by the Major Symptom Score (MSS) composite of symptoms (facial pain/pressure/tenderness, sinus headache, rhinorrhoea, post nasal drip and nasal congestion/stuffiness) during the 15 day treatment period (P02683 p < 0.001; P02692 p = 0.038). In P02683, NASONEX Aqueous Nasal Spray 0.05% 200 µg twice daily reduced the MSS score (averaged across the 15 day treatment period) by 55.6% from baseline, whereas placebo treatment reduced the MSS by 45.6%. In P02692, NASONEX Aqueous Nasal Spray 0.05% 200 µg twice daily reduced the MSS score by 48.4% from baseline, whereas placebo treatment reduced the MSS by 41.5%. (Table 1)

Table 1 Change from Baseline AM/PM Days 1-15 Major Symptom Score

	Study P02683		Study P02692	
Treatment (n)	MF 200 µg BID (233)	Placebo (247)	MF 200 µg BID (236)	Placebo (242)
Mean score at baseline	8.29	8.36	7.70	7.72
Mean change in score from baseline	-4.51	-3.75	-3.76	-3.36
Mean % change in score from baseline	-55.6%	-45.6%	-48.4%	-41.5%
P-value vs placebo	<0.001		0.038	

Patients were eligible for study entry only if all signs and symptoms suggestive of bacterial rhinosinusitis were absent. These signs and symptoms were: fever > 38.3°C; persistent severe unilateral facial pain or tooth pain; orbital or periorbital facial swelling; dental involvement; and worsening of symptoms after initial improvement. In addition, patients with severe symptoms (on a scale of mild, moderate or severe) in more than three of the five MSS symptom groups were not eligible for study participation. Thus, study subjects generally had mild or moderate rhinosinusitis, likely of non-bacterial origin. Consistent with this, a 500 mg three times a day amoxicillin arm was not significantly different from placebo in reducing the symptoms of rhinosinusitis as evaluated by the MSS. Overall, fewer subjects treated with NASONEX Aqueous Nasal Spray 0.05% 200 µg twice daily were considered by the treating physician to be treatment failures than those with placebo (p=0.0074). In addition, during the post-treatment follow-up period, the number of recurrences seen with NASONEX was low and comparable to the amoxicillin and placebo treatment groups. Treatment duration beyond 15 days was not evaluated in acute rhinosinusitis.

PAEDIATRIC CLINICAL PROGRAM

The NASONEX paediatric clinical program consisted of three Phase I pharmacology/pharmacodynamic studies, one Phase II dose-ranging study and three Phase III studies. A total of 1084 paediatric patients received NASONEX. The paediatric program was designed to address all relevant safety issues in paediatric patients aged 3 to 11 years. Additionally, the goal of this program was to establish the lowest effective dose and to confirm efficacy in both seasonal allergic rhinitis and perennial allergic rhinitis.

Two of the Phase I studies conducted in children with allergic rhinitis demonstrated no detectable HPA-axis suppression at multiple doses of 50 to 200 µg/day for 7 days or 14 days. The third Phase I study, a knemometry study, showed no evidence of a reduction in short-term lower leg growth velocity in NASONEX-treated subjects (100 or 200 µg/day).

The Phase II dose-ranging study confirmed the lowest effective dose to be 100 µg per day in the treatment of seasonal allergic rhinitis. The three Phase III studies were designed to assess efficacy and safety in perennial allergic rhinitis as well as long-term safety, including an assessment of possible long-term effects on growth.

Compared with placebo, NASONEX 100 µg once daily significantly reduced the symptoms of seasonal allergic rhinitis and perennial allergic rhinitis in paediatric patients aged between 3 and 11 years. In addition, NASONEX 100 µg once daily was not associated with any reduction in growth velocity when administered for one year.

INDICATIONS

NASONEX Aqueous Nasal Spray 0.05% is indicated for the treatment of symptoms associated with seasonal allergic rhinitis and perennial allergic rhinitis and the prophylaxis of seasonal allergic rhinitis in adults, adolescents and children between the ages of 3 and 11 years.

NASONEX Aqueous Nasal Spray 0.05% is also indicated for the treatment of nasal polyps in adult patients 18 years of age and older.

NASONEX Aqueous Nasal Spray 0.05% is indicated for the treatment of symptoms associated with acute rhinosinusitis in patients 12 years of age and older without signs or symptoms of severe bacterial infection.

CONTRAINDICATIONS

- Patients with known hypersensitivity to mometasone furoate or any of the excipients
- Severe nasal infection, especially candidiasis
- Persons with haemorrhagic diathesis or with a history of recurrent nasal bleeding

PRECAUTIONS

NASONEX Aqueous Nasal Spray 0.05% should not be used in the presence of untreated localised infection involving the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal surgery or trauma should not use a nasal corticosteroid until healing has occurred.

Following 12 months of treatment with NASONEX Aqueous Nasal Spray 0.05%, there was no evidence of atrophy of the nasal mucosa. Mometasone furoate tended to reverse the nasal mucosa closer to a normal histological phenotype. As with any long-term treatment, patients using NASONEX Aqueous Nasal Spray 0.05% over several months or longer should be examined periodically for possible changes in the nasal mucosa. If localised fungal infection of the nose or pharynx develops, discontinuance of NASONEX Aqueous Nasal Spray 0.05% therapy or appropriate treatment may be required. Persistence of nasopharyngeal irritation may be an indication for discontinuing NASONEX Aqueous Nasal Spray 0.05%.

NASONEX Aqueous Nasal Spray 0.05% should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections or ocular herpes simplex.

Topical corticosteroids may be absorbed in amounts that can have systemic effects. Use of excessive doses may suppress HPA function. Physicians should be alert for evidence of systemic effects, especially in chronically treated patients.

However, there is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with NASONEX Aqueous Nasal Spray 0.05%. Patients who are transferred from long-term administration of systemically active corticosteroids to NASONEX Aqueous Nasal Spray 0.05% require careful attention. Systemic corticosteroid withdrawal in such patients may result in adrenal insufficiency for a number of months until recovery of HPA axis function. If these patients exhibit signs and symptoms of adrenal insufficiency, systemic corticosteroid administration should be resumed and other modes of therapy and appropriate measures instituted.

During transfer from systemic corticosteroids to NASONEX Aqueous Nasal Spray 0.05%, some patients may experience symptoms of withdrawal from systemically active corticosteroids (eg joint and/or muscular pain, lassitude and depression initially) despite relief from nasal symptoms and will require encouragement to continue NASONEX Aqueous Nasal Spray 0.05% therapy. Such transfer may also unmask pre-existing allergic conditions such as allergic conjunctivitis and eczema, previously suppressed by systemic corticosteroid therapy.

Patients receiving corticosteroids who are potentially immunosuppressed should be warned of the risk of exposure to certain infections (eg chickenpox, measles) and of the importance of obtaining medical advice if such exposure occurs.

Following the use of intranasal aerosolised corticosteroids, instances of nasal septum perforation or increased intraocular pressure have been reported very rarely.

Safety and efficacy of NASONEX Nasal Spray 0.05% for the treatment of nasal polyposis in children and adolescents less than 18 years of age have not been studied.

Use in acute rhinosinusitis

If signs or symptoms of severe bacterial infection are observed (such as fever, persistent severe unilateral facial/tooth pain, orbital or peri-orbital facial swelling, or worsening of symptoms after an initial improvement), the patient should be advised to consult their physician immediately. If these signs and symptoms are present at the time of diagnosis, treatment with NASONEX should not be initiated.

Safety and efficacy of NASONEX Nasal Spray 0.05% for the treatment of symptoms of acute rhinosinusitis in children under 12 years of age have not been studied.

Effects on Fertility

As with other corticosteroids, at exposure levels associated with marked signs of systemic corticosteroid toxicity, mometasone furoate had progestogenic effects on the female reproductive tract and mammary glands. However, fertility was unimpaired in a reproductive toxicity study carried out in rats.

Use in Pregnancy (Category B3)

In animal studies, small quantities of mometasone furoate were found to cross the placenta barrier. Like other corticosteroids, at doses associated with signs of systemic toxicity, mometasone furoate reduced fetal growth and was teratogenic in mice, rats and rabbits after subcutaneous or topical application. Higher doses had progestogenic effects in pregnant rats, associated with prolonged gestation, dystocia and reduced pup survival.

There are no adequate or well-controlled studies in pregnant women. Low levels of systemic mometasone have been measured following nasal administration of NASONEX Aqueous Nasal Spray 0.05%.

As with other nasal corticosteroid preparations, NASONEX Aqueous Nasal Spray 0.05% should be used in pregnant women only if the potential benefit justifies the potential risk to the mother or fetus. Infants born of mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.

Use in Lactation

After oral administration, small quantities of mometasone furoate and/or its metabolites were transferred into the milk of lactating rats. There are no data on the extent of passage of mometasone furoate and/or its metabolites into the breast milk of women using mometasone furoate nasal spray 0.05%. As with other nasal corticosteroid preparation, NASONEX should be used by lactating mother only if the potential benefit justifies any potential risk to the infant.

Paediatric Use

Controlled clinical trials have shown that intranasal corticosteroids may cause a reduction in growth velocity in children. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in children than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied.

The growth of children receiving intranasal corticosteroids should be monitored routinely (eg. via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits and the availability of safe and effective non-corticosteroid alternatives. To minimise the systemic effects of intranasal corticosteroids, each patient should be titrated to his/her lowest effective dose.

However, no reduction in growth velocity was observed in a placebo-controlled clinical trial in which paediatric patients were administered NASONEX Aqueous Nasal Spray 0.05% 100 µg daily for one year. The effects of treatment for periods of greater than one year have not been studied.

Genotoxicity

Mometasone furoate is not considered to be genotoxic. There was no evidence of mutagenicity in *in vitro* tests which included tests for reverse mutation in *Salmonella typhimurium* and *Escherichia coli* and forward gene mutation in a mouse lymphoma cell line. Limited evidence of clastogenicity was obtained in Chinese Hamster ovary cells, although this finding was not confirmed in a second assay in Chinese Hamster lung cells *in vitro*, nor *in vivo* assays including a chromosomal aberration assay in mouse spermatogonia, a mouse micronucleus assay or in a rat bone marrow clastogenicity assay. Mometasone furoate did not cause DNA damage in rat liver cells.

INTERACTIONS WITH OTHER MEDICINES

There have been no formal interaction studies performed.

ADVERSE EFFECTS

Adult Population

Treatment-related local adverse events reported in clinical studies include headache (8%), epistaxis (i.e. frank bleeding, blood-tinged mucus and blood flecks) (8% vs placebo 5%), nasal burning (2% vs placebo 3%), and nasal irritation (2% vs placebo 2%) and nasal ulceration, which are typically observed with the use of a corticosteroid nasal spray. Epistaxis was generally self-limiting and mild in severity, and occurred at a comparable or lower incidence compared to other active control nasal corticoids used in clinical studies (up to 15%). The incidence of all other effects was comparable with that of placebo.

In the elderly, the more common adverse events were epistaxis (12% vs placebo 5%), headache (9% vs placebo 6%) and pharyngitis (4% vs placebo 2%).

In patients treated for nasal polyposis, the overall incidence of adverse events was comparable to placebo and similar to that observed for patients with allergic rhinitis.

Paediatric Population

In the paediatric population, the most common adverse effects were epistaxis (6% vs placebo 6%), headache (3% vs placebo 4%), nasal irritation (2% vs placebo 1%) and sneezing (2% vs placebo 4%).

Rarely, immediate hypersensitivity reactions (eg. bronchospasm, dyspnea) may occur after intranasal administration of mometasone furoate monohydrate. Very rarely, anaphylaxis and angioedema have been reported.

Disturbances of taste and smell have been reported very rarely.

Growth suppression has been reported in association with administration of intranasal corticosteroids (see PRECAUTIONS, *Use in Children*).

Acute rhinosinusitis

In patients treated for acute rhinosinusitis, the overall incidence of adverse events was comparable to placebo and similar to that observed for patients with allergic rhinitis.

Treatment related adverse events reported most frequently in the NASONEX 200 µg twice daily group include epistaxis (3.7% vs. placebo 2.6%), diarrhoea (2.1% vs. placebo 0.8%), headache (1.7% vs. placebo 2.4%), nausea (1.7% vs. placebo 0.6%) and abdominal pain (1.7% vs. placebo 1.0%).

DOSAGE AND ADMINISTRATION

DO NOT EXCEED THE RECOMMENDED DOSAGE.

The effect of NASONEX Aqueous Nasal Spray 0.05% is not immediate. Full therapeutic benefit takes a few days to develop. Dosage should be administered as directed and not be taken by the patients at will for symptomatic relief.

Administration to young children should be aided by an adult.

Allergic Rhinitis

In patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis, prophylactic treatment with NASONEX is recommended two to four weeks prior to the anticipated start of the pollen season.

Adults (including geriatric patients) and children 12 years of age and over: The usual recommended dose for prophylaxis and treatment is two sprays (50 µg/spray) in each nostril once daily (total daily dose 200 µg). Once symptoms are controlled, reducing the dose to one spray in each nostril (total daily dose 100 µg) may be effective for maintenance.

After the first dose of NASONEX, clinically significant improvement of symptoms was achieved within 12 hours in 28% of a group of patients (n=190) with seasonal allergic rhinitis (median = 36 hours). However, the full benefit of treatment may not be achieved in the first 48 hours, therefore, the patient should continue regular use to achieve full therapeutic benefit.

Children between the ages of 3 and 11 years: The usual recommended dose is one spray (50 µg/spray) in each nostril once daily (total daily dose 100 µg).

Nasal Polyposis

Adults (including geriatric patients) and adolescents 18 years of age and older: The usual recommended dose for polyposis is two sprays (50 micrograms/spray) in each nostril once daily (total daily dose of 200 mcg). If symptoms are inadequately controlled, the dose may be increased to a daily dose of two sprays in each nostril twice daily (total daily dose of 400 micrograms). Dose reduction is recommended following control of symptoms

Acute rhinosinusitis

The usual recommended dose for acute rhinosinusitis is two sprays (50 micrograms/spray) in each nostril twice daily (total daily dose of 400 micrograms). If no improvement is seen after 15 days of twice daily administration, alternative therapies should be considered. If symptoms worsen during treatment, the patients should be advised to consult their physician.

Instructions to patients: Shake container well before each use. **Do not** pierce the nasal applicator. After the initial priming of the NASONEX Aqueous Nasal Spray 0.05% pump (10 actuations, until a uniform spray is observed), each actuation delivers approximately 100 mg of mometasone furoate suspension, containing mometasone furoate monohydrate equivalent to 50 µg of mometasone furoate. If the spray pump has not been used for 14 days or longer, it should be reprimed with 2 actuations, until a uniform spray is observed, before the next use.

OVERDOSAGE

Because the systemic bioavailability of NASONEX Aqueous Nasal is low and has been estimated as <1%, overdose is unlikely to require any therapy other than observation. Treatment can be reinitiated at the usual recommended dose.

Inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of hypothalamic-pituitary-adrenal (HPA) axis function.

PRESENTATION AND STORAGE CONDITIONS

NASONEX Aqueous Nasal Spray 0.05%: is supplied in a HDPE Pump Actuated Metered Dose Aerosol containing mometasone furoate (as the monohydrate) 50 µg/actuation; 1 x 40* metered doses, 1 x 65 metered doses (junior pack), 1 x 140 metered doses and 2 x 140 metered doses.

Cleaning your nasal spray: It is important to clean your nasal spray regularly, otherwise it may not work properly. Remove the dust cap and gently pull off the nozzle. Wash the nozzle and dust cap in warm water and then rinse under a running tap. **Do not try to unblock the nasal applicator by inserting a pin or other sharp object as this will damage the applicator and cause you not to get the right dose of medicine.** Allow to dry in a warm place. Push the nozzle back onto the bottle and replace the dust cap. The spray will need to be re-primed with 2 sprays when first used after cleaning.

Store NASONEX Aqueous Nasal Spray 0.05% below 25°C. Do not freeze.

*Not currently marketed in Australia

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

14 February 2001

DATE OF MOST RECENT AMENDMENT

7 July 2014