New Zealand Data Sheet

APO-ATOMOXETINE

1. PRODUCT NAME

Atomoxetine (as hydrochloride)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg or 100 mg of atomoxetine (as hydrochloride), as the active ingredient.

For the full list of excipients see section **6.1 List of excipients.**

3. PHARMACEUTICAL FORM

Atomoxetine hydrochloride is available as capsules for oral administration. The capsules contain a white to off-white powder.

APO-ATOMOXETINE 10mg is hard gelatin capsule with white opaque body and white opaque cap. Imprinted “APO AM10” in black ink.

APO-ATOMOXETINE 18mg is hard gelatin capsule with white opaque body and gold opaque cap. Imprinted “APO AM18” in black ink.

APO-ATOMOXETINE 25mg is hard gelatin capsule with white opaque body and blue opaque cap. Imprinted “APO AM25” in black ink.

APO-ATOMOXETINE 40mg is hard gelatin capsule with blue opaque body and blue opaque cap. Imprinted “APO AM40” in black ink.

APO-ATOMOXETINE 60mg is hard gelatin capsule with gold opaque body and blue opaque cap. Imprinted “APO AM60” in black ink

APO-ATOMOXETINE 80mg is hard gelatin capsule with white opaque body and orange opaque cap. Imprinted “APO AM80” in black ink.

APO-ATOMOXETINE 100mg is hard gelatin capsule with orange opaque body and orange opaque cap. Imprinted “APO AM100” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APO-ATOMOXETINE is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

Instructions for Use/Handling

APO-ATOMOXETINE capsules are not intended to be opened. Atomoxetine hydrochloride is an ocular irritant. In the event of capsule content coming in contact with the eye, the affected eye should be flushed immediately with water, and medical advice obtained. Hands and any potentially contaminated surfaces should be washed as soon as possible.

Initial Treatment

Children and Adolescents up to 70 kg Body Weight

APO-ATOMOXETINE should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of three days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After an additional two to four weeks, the total daily dose may be increased to a maximum of 1.4 mg/kg in patients who have not achieved an optimal response (see **5.1 Pharmacodynamic properties -** Clinical Trials). The maximum recommended total daily dose in children and adolescents is 1.4 mg/kg or 100 mg, whichever is less.

Children and Adolescents over 70 kg Body Weight and Adults

APO-ATOMOXETINE should be initiated at a total daily dose of 40 mg and increased after a minimum of three days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After an additional two to four weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response (see **5.1 Pharmacodynamic properties - Clinical Trials**). The maximum recommended total daily dose in children and adolescents over 70 kg is 100 mg.

Interrupted Treatment

If therapy is interrupted for more than 1 week, treatment should be started at the recommended starting dose. **(see 4.2 Dose and method of administration, Initial Treatment).**

Maintenance/Extended Treatment

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with APO-ATOMOXETINE. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use APO-ATOMOXETINE for extended periods should periodically re-evaluate the long-term usefulness of the medicine for the individual patient.

Renal or Hepatic Impairment

For those ADHD patients who have hepatic insufficiency or end stage renal disease, cautious titration of APO-ATOMOXETINE to the desired clinical response is recommended **(see 5.2 Pharmacokinetic properties**). APO-ATOMOXETINE clearance may be reduced in patients with hepatic insufficiency. APO-ATOMOXETINE may exacerbate hypertension in patients with end stage renal disease.

General Dosing Information

APO-ATOMOXETINE is intended for oral administration and may be taken with or without food. The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

APO-ATOMOXETINE may be discontinued without tapering the dose.

Maximum Tolerated Daily Dose

The maximum recommended total daily dose in children and adolescents is 1.4 mg/kg or 100 mg, whichever is less. The maximum recommended total daily dose in children and adolescents over 70 kg is 100 mg.

4.3 CONTRAINDICATIONS

Hypersensitivity

APO-ATOMOXETINE is contraindicated in patients with known hypersensitivity to atomoxetine or any excipient in this product.

Monoamine Oxidase Inhibitors

APO-ATOMOXETINE should not be taken with monoamine oxidase inhibitors (MAOIs) or within two weeks after discontinuing MAOIs. Treatment with MAOIs should not be initiated within two weeks after discontinuing APO-ATOMOXETINE.

With other medicines that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal, reactions when taken in combination with MAOIs. These reactions include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these medicines are given concurrently or in close proximity.

Narrow Angle Glaucoma

In clinical studies, the use of atomoxetine was associated with an increased risk of mydriasis and therefore atomoxetine is not recommended in patients with narrow angle glaucoma.

Severe Cardiovascular Disorders

Atomoxetine should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate that could be clinically important (for example, 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate). (Also see section **4.4 Special warnings and precautions for use - Cardiovascular effects**).

Symptomatic cardiovascular disease

moderate to severe hypertension, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, or ventricular flutter, advanced arteriosclerosis (**Also see section 4.4 Special warnings and precautions for use, Precautions)**

Uncontrolled hyperthyroidism

Phaeochromocytoma

APO-ATOMOXETINE should not be used in patients with pheochromocytoma or a history of pheochromocytoma (Also see section **4.4 Special warnings and precautions for use, Precautions**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

Suicidal Ideation and Behaviour

Short-term placebo controlled studies evaluated over 2200 children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD). Among the 1357 patients on atomoxetine, there was a positive signal for suicidal thoughts (5 patients) and behaviours (1 patient) in children 12 years of age and younger compared to placebo (0/851). No suicides occurred in

these trials. Anyone considering the use of atomoxetine in children must balance the risk of suicidality (suicidal thoughts or behaviours) against the clinical need. Patients who are started on atomoxetine should be closely monitored for suicidality (see **4.4 Special warnings and precautions for use, Precautions**).

Allergic Reactions

Although uncommon, allergic reactions, including anaphylactic reactions, rash, angioneurotic oedema and urticaria, have been reported in patients taking atomoxetine.

Hepatic Effects

Post-marketing reports indicate that atomoxetine can cause severe liver injury in rare cases, including acute liver failure. Very rarely, spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported. More than 2 million patients have received atomoxetine during the first two years of global post-marketing experience. During such time, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors. In one of these cases, liver injury recurred upon rechallenge, and was followed by recovery upon drug discontinuation. The patients described above recovered from their liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped.

As with other medications which can cause severe drug-related liver injury, it is possible that a small percentage of patients may progress to acute liver failure resulting in death or the need for a liver transplant.

APO-ATOMOXETINE should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted. Laboratory testing to determine liver enzyme levels should be conducted on the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms).

Precautions

Suicidal Ideation and Behaviour

Suicidal ideation (suicidal thoughts) was statistically more frequently observed in clinical trials among children and adolescents treated with atomoxetine (5/1357; [0.37%]) compared to those treated with placebo (0/851; [0%]). There was one report of suicidal behaviour in a patient in this age group treated with atomoxetine compared with no reports in patients treated with placebo. All reports of suicidal ideation or behaviour in this age group occurred in children 12 years of age or younger. No suicides occurred during these trials. All patients being treated with APO-ATOMOXETINE should be observed for emergence of suicidal thoughts or behaviours, especially during the initial few months of treatment or at times of dose changes. Families and caregivers of children and adolescents being treated with atomoxetine should be informed of the need to monitor these patients for emergence of suicidal thoughts or behaviours that may include signs of agitation, irritability or unusual changes of behaviour. If any of these symptoms develop medical advice should be sought immediately.

Aggressive Behaviour or Hostility

Hostility (predominantly aggression, oppositional behaviour and anger) and emotional lability are often observed in patients with ADHD and have been reported in clinical trials and post-marketing experience for some ADHD medications. Although there is no conclusive evidence that atomoxetine causes aggressive behaviour or hostility, during clinical trials these events were more frequently observed in children, adolescents and adults treated with atomoxetine compared to those receiving placebo (not statistically significant). Patients beginning treatment for ADHD should be monitored for the appearance or worsening of aggressive behaviour or hostility.

Seizures

The pre-clinical and clinical trial data for atomoxetine do not suggest that atomoxetine is proconvulsive. However, seizures have been very rarely reported in post-marketing spontaneous reports. Atomoxetineshould be used with caution in patients with a history of seizures. Discontinuation of atomoxetine should be considered in any patient developing seizures or if there is an increase in seizure frequency where no other cause is identified.

Cardiovascular Effects

APO-ATOMOXETINE can affect heart rate and blood pressure. It is recommended that the heart rate and blood pressure be measured before treatment is started and periodically during treatment to detect possible clinically important increases.

Most patients taking atomoxetine experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) that are not clinically important (See **4.8 Undesirable effects**). However, data from ADHD clinical trials show that some patients (approximately 5 to 10% of children and adults) do experience clinically important changes in heart rate (20 beats per minute or greater) or blood pressure (15 to 20 mm Hg or greater).

Atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. It should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or heart rate that could be clinically important. (See **4.3 CONTRAINDICATIONS**)

APO-ATOMOXETINE should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or heart rate that could be clinically important. (See **4.3 CONTRAINDICATIONS**).

In addition, APO-ATOMOXETINE should be used with caution in patients with congenital QT prolongation, acquired QT prolongation (for example, due to concomitant use of a drug that prolongs the QT), or with a family history of QT prolongation. Because orthostatic hypotension has also been reported, APO-ATOMOXETINE should be used with caution in any condition that may predispose patients to orthostatic hypotension, or conditions associated with abrupt heart rate or blood pressure changes (See **4.3 CONTRAINDICATIONS**)

Hyperthyroidism

APO-ATOMOXETINE should be used with caution in patients with a history of hyperthyroidism.

Sudden Death and Pre-existing Structural Cardiac Abnormalities

Sudden death has been reported in association with some CNS stimulatory drugs used for ADHD treatment at usual doses in children with structural cardiac abnormalities.

A pharmacological potential exists for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: *a)* are involved in strenuous exercise or activities, *b)* use stimulants, or *c)* have a family history of sudden/cardiac death. APO-ATOMOXETINE is a drug with peripheral sympathomimetic effects and should not generally be used in children,

adolescents, or adults with known structural cardiac abnormalities. Prior to the initiation of treatment, a personal and family history should be obtained. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered.

Effects on Co morbid Chronic Tics or Tourette's Disorder

A randomised, double-blind study of atomoxetine and placebo in paediatric outpatients with ADHD and co morbid tic disorders showed that atomoxetine did not worsen tics in patients with ADHD and co morbid chronic motor tics or Tourette's Disorder.

There have been very rare postmarketing reports of tics with atomoxetine treatment.

Effects on Comorbid Anxiety

Two randomised, double-blind, placebo-controlled studies of atomoxetine, one in children and adolescents with ADHD and comorbid anxiety and one in adults with comorbid social anxiety disorder, showed that atomoxetine did not worsen anxiety in patients with ADHD and comorbid anxiety.

There have been rare postmarketing reports of anxiety with atomoxetine treatment.

Effects on Comorbid Major Depressive Disorder

In a controlled study of adolescent patients with ADHD and comorbid major depressive disorder, atomoxetine treated patients did not experience worsening of depression compared to placebo-treated patients. There have been rare postmarketing reports of depression or depressed mood with atomoxetine treatment.

Hepatic Insufficiency

See section **5.2 Pharmacokinetic properties and 4.2 Dose and method of administration** .

Renal Insufficiency

See section **5.2 Pharmacokinetic properties and 4.2 Dose and method of administration**).

In adult ADHD controlled trials, the rates of urinary retention and urinary hesitation were increased among atomoxetine treated patients compared with placebo patients. A complaint of urinary retention or urinary hesitancy should be considered potentially related to atomoxetine.

Paediatric Use

The safety and efficacy of atomoxetine in paediatric patients less than 6 years of age have not been established. The efficacy of atomoxetine beyond 18 months and safety of atomoxetine beyond two years of treatment have not been systematically evaluated.

Use in the elderly

The safety and efficacy of atomoxetine in elderly patients have not been established.

Medicine Abuse and Dependence

Atomoxetine is not a controlled substance and is not a stimulant. In a randomised, double-blind, placebo-controlled, abuse-potential study in adults comparing effects of atomoxetine and placebo, atomoxetine was not associated with a pattern of response that suggested stimulant or euphoriant properties.

Clinical study data in over 2000 children, adolescents and adults with ADHD and over 1200 adults with depression did not demonstrate any pattern of medicine diversion or inappropriate self-administration associated with atomoxetine. There was no evidence of symptom rebound or adverse events suggesting a medicine-discontinuation or withdrawal syndrome.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORM OF INTERACTIONS

Atomoxetine did not cause clinically significant inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6 and CYP2C9. Atomoxetine is principally metabolised by the CYP2D6 pathway. In CYP2D6 extensive metabolisers, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metabolisers.

In vitro studies suggest that co-administration of cytochrome P450 inhibitors to CYP2D6 poor metabolisers will not increase the plasma concentrations of atomoxetine.

Slower titration of atomoxetine may be necessary in those patients who are also taking CYP2D6 inhibitor medicines.

Midazolam
Co-administration of atomoxetine with midazolam resulted in small increases in midazolam plasma concentrations. These changes were smaller than those caused by weak inhibitors of CYP3A and therefore, no dose adjustment is recommended for medicines metabolised by CYP3A.

Methylphenidate
Co-administration of methylphenidate with Atomoxetine did not increase cardiovascular effects beyond those seen with methylphenidate administration alone.

Monoamine Oxidase Inhibitors
APO-ATOMOXETINE should not be taken with monoamine oxidase inhibitors (MAOIs) or within two weeks after discontinuing MAOIs. Treatment with MAOIs should not be initiated within two weeks after discontinuing APO-ATOMOXETINE. (See **4.3 Contraindications** section for further information.)

Anti-hypertensive drugs and Vasopressor Agents
Because of possible effects on blood pressure, APO-ATOMOXETINE should be used cautiously with Anti-hypertensive drugs and vasopressor agents or other drugs that increase blood pressure.

Medicines that Affect Noradrenaline
Medicines that affect noradrenaline should be used cautiously when co-administered with APO-ATOMOXETINE because of the potential for additive or synergistic pharmacological effects

Beta-Adrenergic Receptor Agonists
APO-ATOMOXETINE should be administered with caution to patients being treated with systemically-administered salbutamol (or other beta2 agonists) because the action of salbutamol on the cardiovascular system can be potentiated.

Tricyclic Antidepressants
APO-ATOMOXETINE can increase the adverse cardiovascular effects of tricyclic antidepressants if co-administered.

Desipramine (a tricyclic antidepressants) pharmacokinetics, which are dependent on CYP2D6 metabolism, were not altered by steady-state atomoxetine concentrations. However, because desipramine has noradrenergic effects, these medicines should not be used in combination.

Medicines Highly Bound to Plasma Protein
In vitro medicine-displacement studies were conducted with atomoxetine and other highly bound medicines at therapeutic concentrations. Atomoxetine did not affect the binding of warfarin, acetylsalicylic acid, phenytoin or diazepam to human albumin. Similarly, these compounds did not affect the binding of atomoxetine to human albumin.

Medicines that Affect Gastric pH
Medicines that elevate gastric pH (magnesium hydroxide/aluminium hydroxide, omeprazole) had no effect on atomoxetine bioavailability.

Alcohol
Consumption of ethanol with APO-ATOMOXETINE does not change the intoxicating effects of ethanol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Atomoxetine did not impair fertility when administered to rats from 10 days of age through adulthood at oral doses up to 50 mg/kg/day (up to 7 times the maximum recommended daily oral dose in children and 4 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis). In addition, no evidence of impaired fertility was observed in either of two fertility studies in adult rats provided atomoxetine hydrochloride in the diet at time-weighted average doses up to 57 mg/kg/day (up to 8 times the maximum recommended daily oral dose in children and 5 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis).

Use in Pregnancy

Pregnancy Category B3

No evidence of medicine-associated teratogenicity or retarded foetal development was produced in rabbits or rats administered atomoxetine throughout organogenesis at oral doses up to 100 mg/kg/day and 150 mg/kg/day (at least 20 times the maximum recommended daily oral dose in children and 13 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis). In a rat fertility study, decreased pup weight and survival was observed, predominantly during the first week postpartum following maternal dietary atomoxetine time-weighted average doses of 23 mg/kg/day or higher. No adverse effects were observed in surviving pups.

No adequate and well-controlled studies have been conducted in pregnant women. APO-ATOMOXETINE should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Caution should be exercised if APO-ATOMOXETINE is administered to a nursing woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by Atomoxetine

New Zealand Data Sheet

APO-ATOMOXETINE

4.8 Undesirable Effects

Child and Adolescent Clinical Trials

The most commonly observed adverse events associated with the use of atomoxetine (incidence of 2% or greater) and not observed at an equivalent incidence among placebo- treated patients (atomoxetine incidence at least twice placebo) are listed in Table 1.

Table 1

Treatment-Emergent Adverse Effects Associated with the Use of Atomoxetine in Acute (up to 9 weeks) Child and Adolescent Trials		
Adverse Effect	**Percentage of Patients Reporting**	
System Organ Class/Adverse Effect	**Atomoxetine (n=425)**	**Placebo (n=292)**
Gastrointestinal Disorders		
Constipation	2	1
Dyspepsia	4	1
Infections and Infestations		
Influenza	2	1
Metabolism and Nutritional Disorders		
Appetite decreased	14	6
Nervous System Disorders		
Dizziness	6	2
Psychiatric Disorders		
Mood swings	2	1
Skin and Subcutaneous Tissue Disorders		
Dermatitis	4	2

The following events did not meet the above criteria but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: **Very common (≥ 10%):** abdominal pain (including abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort), vomiting, nausea, blood pressure increased, heart rate increased (heart rate and blood pressure are based on measured vital signs), somnolence (including sedation), headache **Common (≥ 1% and < 10%):** anorexia, insomnia (also includes initial insomnia, middle insomnia and terminal insomnia), irritability, mydriasis, pruritus, rash, weight decreased, depression (also includes major depression, depressive symptoms, depressed mood, and dysphoria), fatigue and **Uncommon (≥ 0.1% and < 1%):** flushing, palpitations, sinus tachycardia, conjunctivitis, syncope (also includes syncope vasovagal), tremor, asthenia.

In a post-hoc meta-analysis of the placebo-controlled paediatric clinical trial database, suicidal ideation (suicidal thoughts) was statistically more frequently observed among children and adolescents treated with atomoxetine (5/1357; [0.37%]) compared to those treated with placebo (0/851; [0%]). There was one report of suicidal behaviour in a patient in this age group treated with atomoxetine compared with no reports in patients treated with placebo (see **4.4 Special warnings and precautions for use** – Suicidal Ideation and Behaviour).

The following adverse events occurred in at least 2% of child and adolescent CYP2D6 poor metaboliser (PM) patients and statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: weight decreased (7.3% of PMs, 4.4% of EMs), constipation (6.8% of PMs, 4.3% of EMs), insomnia (11% of PMs, 6.1% of EMs), depression (6.5% of PMs, 4.1% of EMs), tremor (4.5% of PMs, 0.9% of EMs); middle insomnia (2.8% of PMs, 1.3% of EMs); syncope (2.5% of PMs, 0.7% of EMs); conjunctivitis (2.5% of PMs, 1.2% of EMs); early morning awakening (2.3% of PMs, 0.8% of EMs); mydriasis (2.0% of PMs, 0.6% of EMs); sedation (3.9% of PMs, 2.1% of EMs).

Growth – Pediatric patients treated with atomoxetine in ADHD clinical trials had a mean initial decrease in weight and height gain. Subsequently, over the long-term period, patients recovered to the mean weight and height predicted by group baseline data.

Adult Clinical Trials

The most commonly observed adverse events associated with the use of atomoxetine (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (atomoxetine incidence at least twice placebo) are listed in **Table 2** below.

Table 2

Treatment-Emergent Adverse Events Associated with the Use of Atomoxetine in Acute (up to 10 weeks) Adult Trials		
Adverse Event[1]	**Percentage of Patients Reporting Event**	
System Organ Class/Adverse Event	**Atomoxetine (n=269)**	**Placebo (n=263)**
Cardiac Disorders		
Palpitations	4	1
Gastrointestinal Disorders		
Dry mouth	21	6
Nausea	12	5
Constipation	10	4
Flatulence	2	1
General Disorders and Administration Site Conditions		
Rigors	3	1
Investigations		
Weight decreased	2	1
Metabolism and Nutritional Disorders		
Appetite decreased	10	3
Nervous System Disorders		
Dizziness	6	2
Headache	3	1
Psychiatric Disorders		
Insomnia	13	6
Middle insomnia	4	1
Libido decreased	6	2
Sleep disorder	4	2
Renal and Urinary Disorders		
Urinary hesitation	3	0
Urinary retention	3	0
Difficulty in micturition	2	0
Reproductive System and Breast Disorders		
Erectile dysfunction[2]	7	1
Dysmenorrhoea[3]	7	3
Impotence[2]	3	0
Prostatitis[2]	3	0
Orgasm abnormal	2	1
Menstruation irregular[3]	2	0
Skin and Subcutaneous Tissue Disorders		

Hyperhydrosis	4	1
Vascular Disorders		
Hot flush	3	1

[1] Events reported by at least 2% of patients treated with atomoxetine and at least twice the placebo incidence.

[2] Based on total number of males (atomoxetine, n=174; placebo, n=172).

[3] Based on total number of females (atomoxetine, n=95; placebo, n=91).

The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment, **Very common (≥10%)**: blood pressure increased, heart rate increased (heart rate and blood pressure are based on measured vital signs), **Common (≥ 1% and <10%):** abdominal pain (includes abdominal pain upper, stomach discomfort, abdominal discomfort, and epigastric discomfort), rash, dyspepsia, vomiting, asthenia, feeling jittery, irritability, thirst, dysgeusia, somnolence (including sedation), tremor, agitation, pollakuria, flushing, terminal insomnia, ejaculation disorder, ejaculation failure, testicular pain, urine flow decreased, fatigue, lethargy, tachycardia, paraesthesia, chills and **Uncommon (≥0.1% and <1%):** feeling cold, muscle spasms, peripheral coldness, restlessness, micturition urgency, pruritis, urticaria, blurred vision.

The following adverse events occurred in at least 2% of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 extensive metaboliser (EM) patients: vision blurred (3.9% of PMs, 1.3% of EMs); dry mouth (34.5% of PMs, 17.4% of EMs); constipation (11.3% of PMs, 6.7% of EMs); feeling jittery (4.9% of PMs, 1.9% of EMs), decreased appetite (23.2% of PMs, 14.7% of EMs); tremor (5.4% of PMs, 1.2% of EMs); insomnia (19.2% of PMs, 11.3% of EMs); sleep disorder (6.9% of PMs, 3.4% of EMs); middle insomnia (5.4% of PMs, 2.7% of EMs); terminal insomnia (3.0% of PMs, 0.9% of EMs); urinary retention (5.9% of PMs, 1.2% of EMs); erectile dysfunction (20.9% of PMs, 8.9% of EMs); ejaculation disorder (6.1% of PMs, 2.2% of EMs); hyperhidrosis (14.8% of PMs, 6.8% of EMs); peripheral coldness (3.0% of PMs, 0.5% of EMs).

Post-marketing Data

The following list of undesirable effects (adverse drug reactions) is based on post-marketing spontaneous reports, and corresponding reporting rates have been provided.

General Disorders and Administration Site Conditions – Very rare (<0.01%): lethargy.

Investigations – Rare (>0.01% to <0.1%): blood pressure increased.

Psychiatric – Rare (>0.01% to <0.1%): completed suicide, suicide attempt, suicidal ideation, aggression/hostility, psychosis/mania, depression and depressed mood, anxiety. Very rare (<0.01%): sensory disturbances including hallucinations.

Vascular Disorders – Very rare (<0.01%): peripheral vascular instability and/or Raynaud's phenomenon, potential to exacerbate pre-existing Raynaud's phenomenon.

Urogenital System – Very rare (<0.01%): painful or prolonged erection, male genital pain, urinary hesitation in children and adolescents, urinary retention in children and adolescents. **Cardiovascular system** — Very rare (<0.01%): QT prolongation, syncope.

Nervous system – Very rare (<0.01%): seizures, paraesthesia in children and adolescents, hypoaethesia, tics.

Skin and Subcutaneous Disorders – Very rare (<0.01%): Hyperhydrosis.

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 https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Post marketing data has reports of non-fatal acute and chronic overdoses of atomoxetine alone. The most commonly reported symptoms accompanying acute and chronic overdoses were gastrointestinal symptoms, somnolence, dizziness, tremor, and abnormal behaviour. Hyperactivity and agitation have also been reported. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g. tachycardia, blood pressure increased, mydriasis, dry mouth) were also observed. Most events were mild to moderate. In some cases of overdose involving atomoxetine, seizures and very rarely QT prolongation have been reported. There have also been reports of fatal, acute overdoses involving a mixed ingestion of atomoxetine and at least one other drug.

There is limited clinical trial experience with atomoxetine overdose. No fatal overdoses occurred in clinical trials.

Management of Overdose

An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion. Activated charcoal may be useful in limiting absorption. Because atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action APO-ATOMOXETINE is a non-stimulant treatment for Attention-Deficit/Hyperactivity Disorder
(ADHD). [ADHD was formerly known as Attention Deficit Disorder (ADD) with or without hyperactivity.]

Atomoxetine is a potent inhibitor of the pre-synaptic noradrenaline transporter with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. In *ex vivo* uptake and neurotransmitter depletion studies, atomoxetine was found

to selectively inhibit the pre-synaptic noradrenaline transporter without directly affecting the serotonin or dopamine transporters. Atomoxetine has minimal affinity for other receptor systems. Atomoxetine is primarily oxidised to 4-hydroxyatomoxetine, which is also a potent inhibitor of the pre-synaptic noradrenaline transporter.

A thorough QT/QTc study, conducted in healthy adult CYP2D6 poor metabolizer (PM) subjects dosed up to 60 mg of atomoxetine BID, demonstrated that at maximum expected concentrations the effect of atomoxetine on QTc interval was not significantly different from placebo. There was a slight increase in QTc interval with increased atomoxetine concentration.

Clinical Trials

Children and Adolescents

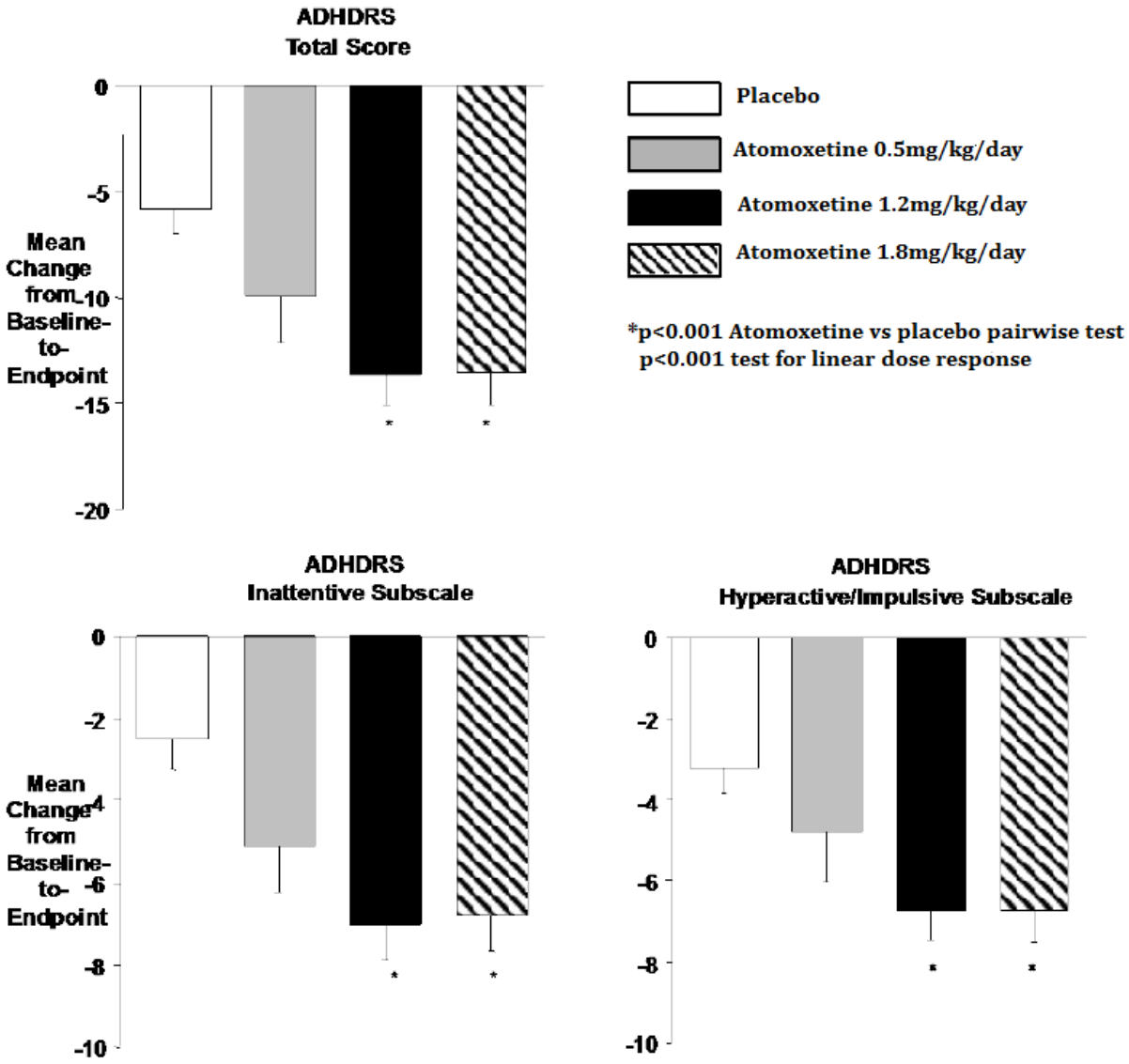
The efficacy of atomoxetine in the treatment of ADHD in children and adolescents was established in four randomised, double-blind, placebo-controlled studies of paediatric patients (ages 6 to 18 years) who met DSM-IV criteria for ADHD.

Approximately one third of the patients met DSM-IV criteria for inattentive subtype and two thirds met criteria for both inattentive and hyperactive/impulsive subtypes.

Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for atomoxetine-treated and placebo-treated patients using an intent-to-treat analysis. The primary outcome measure being the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive subscales. Each item on the ADHDRS maps directly to one symptom criterion for ADHD in the DSM-IV. A second assessment, the Clinical Global Impression Severity (CGI-S) scale, reflects the impression of a skilled observer about the overall clinical state of the patient. The skilled observer was required to be fully familiar with the manifestations of ADHD.

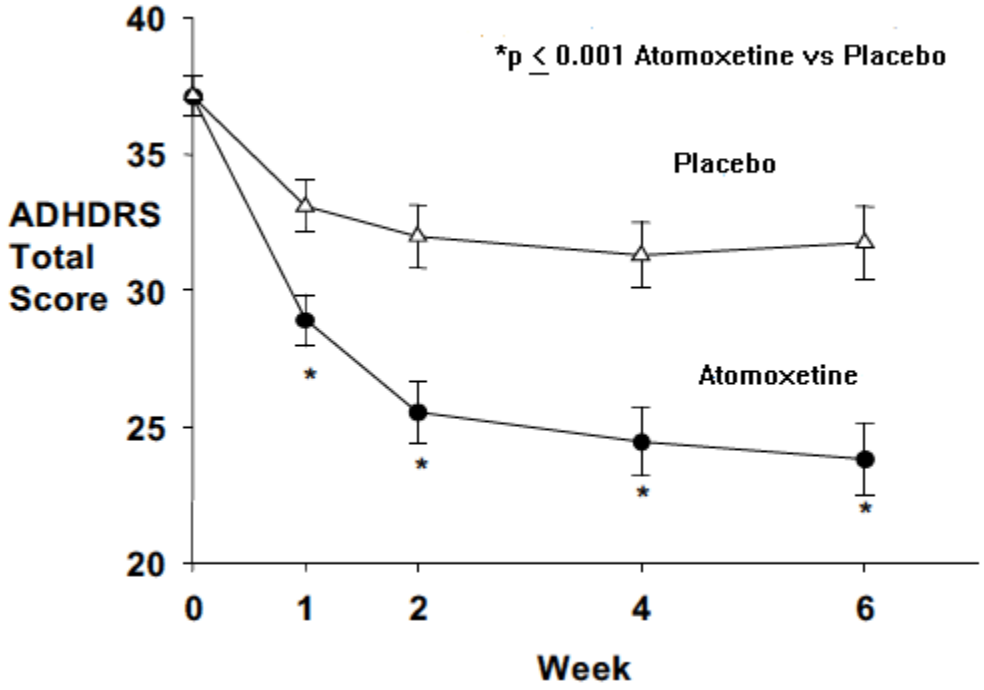
In Study LYAC, an 8-week randomised, double-blind, placebo-controlled acute treatment study of children and adolescents aged 8 to 18 years (n=297), patients received either a fixed dose of atomoxetine (0.5 mg/kg/day, 1.2 mg/kg/day, or 1.8 mg/kg/day) or placebo. Atomoxetine was administered as a divided dose in the early morning and late afternoon/early evening. Treatment with atomoxetine showed an overall improvement in the reductions from baseline in mean ADHDRS total score. The average score decreased by 25% on 0.5 mg/kg/day, 35% on 1.2 mg/kg/day and 34% on 1.8 mg/kg/day atomoxetine, compared to 15% with placebo. At the two higher doses, improvements in ADHD symptoms were superior and statistically significant ($p<0.001$ vs. placebo) in atomoxetine-treated patients compared with placebo-treated patients as measured on the ADHDRS and CGI-S scales. Atomoxetine was effective in reducing both inattentive and hyperactive/impulsive symptoms. The results of Study LYAC are summarised in **Figure 1**.

Figure 1. Atomoxetine Response by Dose.



In Study LYAT, a 6-week randomised, double-blind, placebo-controlled acute treatment study of children and adolescents aged 6 to 16 years (n=171), patients received either atomoxetine or placebo. Atomoxetine was administered as a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response. The maximum atomoxetine dose was 1.5 mg/kg/day. The mean final dose of atomoxetine was approximately 1.3 mg/kg/day. Treatment with atomoxetine showed an overall improvement in the reductions from baseline in mean ADHDRS total score. The average score decreased by 34% on atomoxetine, compared to 13% with placebo ($p<0.001$ vs. placebo). Improvements in ADHD symptoms were superior and statistically significant in atomoxetine treated patients compared with placebo-treated patients as measured on the ADHDRS scale beginning at one week and through the end of the study. Improvements in ADHD symptoms were also superior in atomoxetine treated patients on the CGI-S scale. Atomoxetine was effective in reducing both inattentive and hyperactive/impulsive symptoms. This study demonstrates that atomoxetine is effective when administered once daily in the morning. The results of Study LYAT are summarised in **Figure 2.**

Figure 2. Once-daily administration of atomoxetine



In Study LYAW, a 7-week randomised, double-blind, placebo-controlled acute treatment study of children and adolescents aged 6 to 16 years (n=153), patients received either atomoxetine or placebo. Atomoxetine was administered as a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response. The maximum atomoxetine dose was 1.8 mg/kg/day. The mean final dose of atomoxetine was approximately 1.3 mg/kg/day. Treatment with atomoxetine showed an overall improvement in the reductions from baseline in mean ADHDRS total score based on teacher reports. The average score decreased by 37% on atomoxetine, compared to 19% with placebo ($p<0.001$ vs. placebo). Improvements in ADHD symptoms at school were superior and statistically significant in atomoxetine treated patients compared with placebo-treated patients as measured on the ADHDRS scale beginning at one week and through the end of the study. Improvements in ADHD symptoms were also superior in atomoxetine -treated patients on the CGI-S scale. Atomoxetine was effective in reducing both inattentive and hyperactive/impulsive symptoms. This study demonstrates that atomoxetine is effective when administered once daily in the morning.

In two identical, 9-week, acute, randomised, double-blind, placebo-controlled studies of children aged 7 to 13 years (Study HFBD, n=147; Study HFBK, n=144), atomoxetine or methylphenidate was compared with placebo. The primary comparison of interest in both studies was atomoxetine vs. placebo. Atomoxetine was administered as a divided dose in the early morning and late afternoon (after school) and titrated on a weight-adjusted basis according to clinical response. The maximum recommended atomoxetine dose was 2.0 mg/kg/day. The mean final dose of atomoxetine for both studies was approximately 1.6 mg/kg/day. Treatment with atomoxetine showed an overall improvement from baseline in mean ADHDRS total score. The average score decreased by 38% on atomoxetine, compared to 13% with placebo ($p<0.0001$ vs. placebo) in study HFBD and 38% on atomoxetine, compared to 16% with placebo ($p<0.0003$ vs. placebo) in study HFBK. In both studies, improvements in ADHD symptoms were superior and statistically significant in atomoxetine -treated patients compared with placebo-treated patients as measured on the ADHDRS and

CGI-S scales. Atomoxetine was effective in reducing both inattentive and hyperactive/impulsive symptoms.

Adults

The efficacy of atomoxetine for the treatment of ADHD in adults (18 years of age and older) meeting DSM-IV criteria and with a childhood history of ADHD was established in two, short-term (10 weeks), randomised, double-blind, placebo-controlled studies; and one, long-term (up to 3 years), open-label study. There are no long term, randomised, double-blind, placebo-controlled studies in adults.

Signs and symptoms of ADHD were evaluated using the investigator administered Conners Adult ADHD Rating Scale Screening Version (CAARS), a 30-item scale. The primary efficacy measure was the 18-item Total ADHD Symptom score (the sum of the inattentive and hyperactivity/impulsivity subscales) evaluated by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis.

Studies LYAA and LYAO- In two identical, 10-week, randomised, double-blind, placebo-controlled acute treatment studies (Study LYAA, N=280; Study LYAO, N=256), patients received either atomoxetine or placebo. Atomoxetine was administered as a divided dose in the early morning and late afternoon/early evening and titrated according to clinical response. The maximum atomoxetine dose was 120 mg/day. The mean final dose of atomoxetine for both studies was approximately 95 mg/day. Treatment with atomoxetine showed an overall improvement from baseline in mean CAARS total score. The average score decreased by 28% on atomoxetine, compared to 18% with placebo ($p<0.001$ vs placebo) in study LYAA and 30% on atomoxetine, compared to 20% with placebo ($p<0.001$ vs placebo) in study LYAO. In both studies, improvements in ADHD symptoms were superior and statistically significant in atomoxetine -treated patients compared with placebo-treated patients as measured on the CAARS scale.

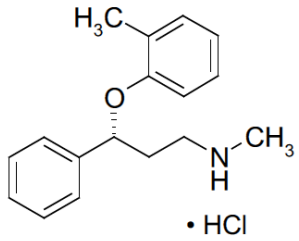
Study LYAR- was an open-label, multi-center investigation of the long-term safety and tolerability of atomoxetine in patients aged 18 years or older who meet the DSM-IV criteria for ADHD. This was an open label extension of the LYAA and LYAO studies. Average symptom severity decreased by 30.6% ($p<0.001$) as measured by the CAARS investigator rated scale for 18 item total ADHD symptoms. The adverse event profile was similar to that observed in short-term studies with most treatment emergent adverse events reported to be of mild or moderate severity.

Examination of population subsets (gender, age, or prior stimulant treatment) did not reveal any differential responsiveness on the basis of these subgroupings.

New Zealand Data Sheet

APO-ATOMOXETINE

Chemical structure



CAS Number

The CAS number for atomoxetine is 82248-59-7.

5.2 Pharmacokinetics PROPERTIES

Single-dose and steady-state individual pharmacokinetic data have been obtained in children, adolescents and adults. After administration of the same mg/kg dose to children, adolescents and adults, similar half-life, mean maximum observed plasma concentration (Cmax) and the extent of oral absorption (AUC) values were observed. Clearance and volume of distribution after adjustment for body weight were also similar.

Absorption

Atomoxetine has high permeability and is rapidly and almost completely absorbed after oral dosing reaching Cmax approximately 1 to 2 hours after dosing. APO-ATOMOXETINE can be administered with or without food. In clinical trials with children and adolescents, administration of APO-ATOMOXETINE with food resulted in a 9% lower C_{max}. Administration of APO-ATOMOXETINE with a standard high-fat meal in adults did not affect the extent of oral absorption of atomoxetine (AUC), but did decrease the rate of absorption resulting in a 37% lower C_{max}. The absolute bioavailability of atomoxetine following oral administration of APO-ATOMOXETINE ranged from 63% to 94% depending upon inter-individual differences in the modest first pass metabolism.

Distribution

The steady-state volume of distribution after intravenous administration was approximately

0.85 L/kg indicating atomoxetine distributes primarily into total body water. In children and adolescents, volume of distribution increased nearly proportionally to increases in body weight. Volume of distribution was similar across the patient weight range after normalising for body weight. At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily albumin.

Metabolism

Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway. The major oxidative metabolite formed is 4-hydroxyatomoxetine, which is rapidly glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine but circulates in plasma at much lower concentrations. Although 4-hydroxyatomoxetine is primarily formed by CYP2D6, in individuals that lack CYP2D6 activity, 4-hydroxyatomoxetine can be formed by several other cytochrome P450 enzymes, but at a slower rate. Atomoxetine does not inhibit or induce the CYP2D6 pathway.

There are two major phenotypes associated with CYP2D6: extensive metabolisers that comprise greater than 90% of the population and poor metabolisers. Co-administration of APO-ATOMOXETINE with known inhibitors of CYP2D6 does not result in an increased sensitivity to APO-ATOMOXETINE, although it may result in higher atomoxetine plasma

exposure. Adjustment of dosing regimens based on metabolism through the CYP2D6 pathway is not necessary.

Excretion

Mean apparent plasma clearance of atomoxetine after oral administration in adult extensive metabolisers is 0.35L/hr/kg and the mean half-life is 3.6 hours. Following oral administration in CYP2D6 poor metabolisers, mean apparent plasma clearance is 0.034 L/hr/kg and mean half-life is 21 hours. At steady state, the AUC of atomoxetine is approximately 10-fold higher and the maximum plasma concentration at steady state ($C_{ss,max}$) is about 5-fold higher in CYP2D6 poor metabolisers than in extensive metabolisers. No statistically significant differences in adverse events or mean efficacious dose were observed between extensive and poor metabolisers, although variability was observed in drug clearance across the population studied. Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-O- glucuronide, mainly in the urine (greater than 80% of the dose) and to a lesser extent in the faeces (less than 17% of the dose). Only a small fraction of the APO-ATOMOXETINE dose was excreted as unchanged atomoxetine (less than 3% of the dose), indicating extensive biotransformation.

Special Populations

Hepatic Insufficiency

In clinical trials single doses of atomoxetine were administered to subjects with moderate to severe hepatic insufficiency (Child-Pugh Class B and C) resulting in reduced atomoxetine clearance, increased atomoxetine exposure (AUC) and prolonged half-life of parent drug compared with healthy subjects. However, the maximum exposure observed in subjects with hepatic insufficiency did not exceed that observed in the population of healthy CYP2D6 poor metabolisers. For those ADHD patients who have hepatic insufficiency, cautious titration of APO-ATOMOXETINE to the desired clinical response is recommended.

Renal Insufficiency

In clinical trials single doses of atomoxetine were administered to subjects with end stage renal disease, resulting in higher atomoxetine exposure (AUC) than in healthy subjects. However, the maximum exposure observed in subjects with end stage renal disease did not exceed that observed in the population of healthy CYP2D6 poor metabolisers. APO-ATOMOXETINE may exacerbate hypertension in patients with end stage renal disease. For those ADHD patients who have end stage renal disease, cautious titration of APO-ATOMOXETINE to the desired clinical response is recommended, with particular attention to those with hypertension that may experience deterioration in the control of their blood pressure.

5.3 Preclinical safety data

Carcinogenicity

There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility from *in vitro* and animal studies with atomoxetine. Atomoxetine was not carcinogenic in rats and mice when given in the diet for 2 years at time-weighted average doses up to 47 and 458 mg/kg/day. These doses are approximately 6 (rat) and 31 (mouse) times the maximum recommended daily oral dose in children and approximately 4 (rat) and 20 (mouse) times the maximum recommended daily oral dose in adults, on a mg/m^2 basis.

Mutagenicity

Atomoxetine was not mutagenic in a battery of tests including the following: Ames and gradient plate bacterial mutation assays, mouse lymphoma cell mutation assay, chromosomal aberration test in Chinese hamster ovary cells, *in vivo* micronucleus test in mice, unscheduled DNA synthesis test in rat hepatocytes and *in vivo* sister chromatid exchange test in bone marrow of Chinese hamsters.

New Zealand Data Sheet

APO-ATOMOXETINE

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- gelatin
- pregelatinised maize starch
- titanium dioxide
- iron oxide yellow (18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg)
- iron oxide red (80 mg, 100 mg)
- indigo carmine (25 mg, 40 mg, 60 mg)

The capsules are printed with edible black ink (TekPrint SW-9008 Black Ink/TekPrint SW-9009 Black Ink).

6.2 INCOMPATIBILITIES

Nil

6.3 SHELF-LIFE

Shelf life: 2 years from the date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C. Store in original container

6.5 NATURE OF CONTENTS OF CONTAINER

Blister packs of 28 capsules: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg Bottles of 1000 capsules for all strengths

Not all strengths, pack types and/or pack sizes may be available

7. Medicine Schedule

Prescription Medicine

8. Sponsor Details

Arrotex Pharmaceuticals (NZ) Limited:

Address: C/o Quigg Partners

Level 7, The Bayleys Building

36 Brandon Street,

Wellington 6011, New Zealand

Distributor

Pharmacy Retailing (NZ) Ltd trading as Healthcare Logistics

58 Richard Pearse Drive

Airport Oaks

Auckland

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Tel: +64 9 918 5100

9. DATE OF FIRST APPROVAL

22 August 2014

10. Date OF REVISION OF THE TEXT

04 November 2021