NEW ZEALAND DATA SHEET

1. PRODUCT NAME
CLONIDINE (Teva) 25 microgram tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains clonidine hydrochloride 25 micrograms.

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
White to off-white circular tablet, engraved with 'CD 25' on one side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
The prophylactic management of migraine or recurrent vascular headaches in adult patients.

The management of vasomotor conditions commonly associated with menopause and characterised by flushing.

4.2 Dose and method of administration
Dose

Adults (including elderly patients)
Therapy should be started with one tablet twice daily (morning and evening).

If there is no relief after two weeks the dosage can be gradually increased to 3 tablets twice daily.

Duration of treatment will depend on the frequency and severity of attacks. It may take 2 - 4 weeks until Clonidine (Teva) is fully effective.

Note: Clonidine (Teva) is not suitable for clearing acute migraine headaches.

Special populations

Renal impairment
Clonidine should be used with caution in patients with renal insufficiency. Careful monitoring of blood pressure is required.

Paediatric population

The safety and efficacy of clonidine in children and adolescents have not been established.

4.3 Contraindications
Clonidine (Teva) should not be used in patients with known hypersensitivity to the active ingredient or other components of the product, and in patients with severe bradyarrhythmia resulting from either sick sinus syndrome or AV blocks of 2nd or 3rd degree.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see section 4.4 Special warnings and precautions for use) the use of the product is contraindicated.

4.4 Special warnings and precautions for use
At doses higher than those recommended above, clonidine is an effective antihypertensive agent. Caution should be observed where antihypertensive agents are being used, as potentiation of the

hypotensive effect may occur. Provided the recommended dosage regimen is followed, no difficulty with hypotension should arise during the routine management of patients with either migraine or menopausal flushing.

Clonidine should be used with caution in patients with mild to moderate bradyarrhythmia, such as low sinus rhythm, with disorders of cerebral or peripheral perfusion (e.g. Raynaud's disease), depression, polyneuropathy and constipation.

Clonidine and its metabolites are extensively excreted with the urine. Clonidine should therefore be used with caution in patients with renal insufficiency (see section 4.2 Dose and method of administration).

As with other antihypertensive drugs, treatment with clonidine should be monitored particularly carefully in patients with heart failure or severe coronary disease.

In patients who have developed localised skin reaction to patches containing clonidine, substitution of oral clonidine therapy may be associated with the development of a generalised rash.

If long-term treatment with a beta-receptor blocker has to be interrupted, then the beta-receptor blocker should first be phased out gradually and then clonidine.

Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of clonidine after prolonged treatment with high doses, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headaches or nausea have been reported. When discontinuing therapy with clonidine, the physician should reduce the dose gradually over 2 - 4 days. An excessive rise in blood pressure following discontinuation of clonidine therapy can be reversed by intravenous phentolamine or tolazoline (see section 4.5 Interaction with other medicines and other forms of interaction).

Patients who wear contact lenses should be warned that treatment with clonidine may cause decreased lacrimation.

This product contains 48 mg lactose monohydrate per tablet. Patients with the rare hereditary conditions of galactose intolerance (e.g. galactosaemia), the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population
The use and the safety of clonidine in children and adolescents under 18 years have little supporting evidence in randomised controlled trials and therefore cannot be recommended for use in this population (see section 5.1 Pharmacodynamic properties).

In particular, when clonidine is used off-label concomitantly with methylphenidate in children with ADHS, serious adverse reactions, including death, have been observed. Therefore, clonidine in this combination is not recommended.

4.5 Interaction with other medicines and other forms of interaction

If clonidine is administered concomitantly with agents such as diuretics, vasodilators, beta-receptor blockers, calcium antagonists or ACE-inhibitors, their hypotensive effect can be potentiated.

Substances with alpha$_2$-receptor blocking properties such as mirtazapine, phentolamine or tolazoline may abolish the alpha$_2$-receptor mediated effects of clonidine in a dose-dependent manner.

Concomitant administration of substances with a negative chronotropic or dromotropic effect such as beta-receptor blockers or digitalis glycosides can cause or potentiate bradycardic rhythm disturbances.

It cannot be ruled out that concomitant administration of a beta-receptor blocker will cause or potentiate peripheral vascular disorders. Studies with combined administration of clonidine and beta-receptor blockers have shown that if treatment is to be discontinued, the dose of the beta-receptor blocker must always be slowly diminished first, followed by the clonidine.

Orthostatic regulation disturbances may be provoked or aggravated by concomitant administration of tricyclic anti-depressants or neuroleptics with alpha-receptor blocking properties. It may be necessary to adjust the dosage of clonidine if these agents are administered concurrently.

The effect of centrally depressant substances or alcohol can be potentiated by clonidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3

There are limited data from the use of clonidine in pregnant women. During pregnancy, clonidine, as any drug, should only be administered if the benefit justifies any possible risks to the foetus. Careful monitoring of mother and child is recommended. Clonidine passes the placenta barrier and may lower the heart rate of the foetus. There is no adequate experience regarding long-term effects of prenatal exposure.

During pregnancy the oral forms of clonidine should be preferred. Intravenous injection of clonidine should be avoided.

Non-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3 Preclinical safety data - Toxicology). Post partum, a transient rise in blood pressure in the newborn cannot be excluded.

Breastfeeding

Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. The use of clonidine is therefore not recommended during breast feeding.

Fertility

No clinical studies on the effect on human fertility have been conducted with clonidine. Non-clinical studies with clonidine indicate no direct or indirect harmful effects with respect to the fertility index (see section 5.3 Preclinical safety data - Toxicology).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness, sedation and accommodation disorder during treatment with cClonidine. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Most adverse effects are mild and tend to diminish with continued therapy. Frequent side effects are dryness of mouth, sedation and reduction of blood pressure.

Endocrine disorders:

gynaecomastia

Psychiatric disorders:

confusional state, delusional perception, depression, hallucination, libido decreased, nightmare, sleep disorder

Nervous system disorders:
dizziness, headache, paraesthesia, sedation

Eye disorder:
accommodation disorder, lacrimation decreased

Cardiac disorders:
atrioventricular block, bradyarrhythmia, sinus bradycardia

Vascular disorders:
orthostatic hypotension, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:
nasal dryness

Gastrointestinal disorders:
colonic pseudo-obstruction, constipation, dry mouth, nausea, salivary gland pain, vomiting. Very rarely pain in the parotid gland.

Skin and subcutaneous tissue disorders:
alopecia, pruritus, rash, urticaria

Reproductive system and breast disorders:
erectile dysfunction

General disorders and administration site conditions:
fatigue, malaise

Investigations:
blood glucose increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
Symptoms
Clonidine has a wide therapeutic range. The symptoms of overdosage are due to generalised sympathetic depression and include pupillary constriction, lethargy, bradycardia, hypotension, somnolence including coma, respiratory depression including apnoea. Paradoxic hypertension caused by stimulation of peripheral alpha$_1$-receptors may occur.

Treatment
Careful monitoring and symptomatic measures.

Gastric lavage and/or administration of activated charcoal should be performed where appropriate.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antimigraine preparations, ATC code: N02CX02

Mechanism of action
Clonidine is a centrally acting α_2-agonist. The central inhibiting effect on noradrenergic neurotransmission generally dominates the peripheral excitatory α_2-effect.

In the prophylaxis of migraine, based on observations that vascular responsiveness is reduced after long-term administration of low doses of clonidine, a hypothesis of a peripheral mode of action has been put forward. The reduced responsiveness of the vessels to adrenergic stimuli due to clonidine possibly also plays a significant role in the reduction of menopausal hot flushes. Central as well as peripheral mode of action are discussed as affecting climateric complaints, e.g. reduced noradrenergic activity in the hypothalamus and changes in central hormone secretion.

Paediatric population
There were two small paediatric studies in migraine, neither of which demonstrated efficacy. In paediatric studies the most frequent adverse events were drowsiness, dry mouth, headache, dizziness and insomnia. These adverse events might have serious impact on daily functioning in paediatric patients.

5.2 Pharmacokinetic properties

Absorption
The pharmacokinetics of clonidine is dose-proportional in the range of 75 - 300 mcg. Clonidine is well absorbed and undergoes a minor first pass effect. Peak plasma concentrations are reached within 1 - 3 h after oral administration. The plasma protein binding is 30 - 40%.

Distribution
Clonidine is rapidly and extensively distributed into tissues and crosses the blood brain barrier, as well as the placental barrier. Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns

Biotransformation
The terminal elimination half-life of clonidine has been found to range from 5 to 25.5 hours. It can be prolonged in patients with severely impaired renal function up to 41 hours. About 70% of the dose administered is excreted with the urine mainly in form of the unchanged parent drug (40-60% of the dose). The main metabolite p-hydroxy-clonidine is pharmacologically inactive.

Elimination
Approximately 20% of the total amount is excreted with the faeces. The pharmacokinetics of clonidine is not influenced by food or by the race of the patient.

The antihypertensive effect is reached at plasma concentrations between about 0.2 and 2.0 ng/ml in patients with normal renal function. The hypotensive effect is attenuated or decreases with plasma concentrations above 2.0 ng/mL.

5.3 Preclinical safety data

Toxicology
Single dose toxicity studies with clonidine were performed in different animal species by oral and parenteral routes of administration. The approximate oral LD_{50} values were 70 mg/kg (mouse), 190 mg/kg (rat), > 15 mg/kg (dog), and 150 mg/kg in monkeys. Following subcutaneous injection, the LD_{50} values were > 3 mg/kg in dogs and 153 mg/kg in rats. After intravenous administration the lethal dose ranges were between 6 mg/kg (dog) and < 21 mg/kg (rat).

Toxic trans-species signs of toxicity following exposure to clonidine were exophthalmus, ataxia and tremor, independently from the route of administration. At lethal doses, tonic-clonic convulsions occurred. In addition, excitement and aggressiveness alternating with sedation (mouse, rat, dog), salivation and tachypnea (dog) as well as hypothermia and apathy (monkey) were observed.

In repeated oral dose toxicity studies up to 18 months clonidine was well tolerated at 0.1 mg/kg (rat), 0.03 mg/kg (dog) and 1.5 mg/kg (monkey). In a 13 week study in rats, the no adverse effect level (NOAEL) was 0.05 mg/kg following subcutaneous administration. After intravenous administration rabbits and dogs tolerated 0.01 mg/kg/day for 5 and 4 weeks, respectively. Higher dosages caused hyperactivity, aggression, reduced food consumption and body weight gain (rat), sedation (rabbit) or an increase in heart and liver weight accompanied by elevated serum GPT, alkaline phosphatase and alpha-globulin levels and focal liver necroses (dog).

There were no signs of any teratogenic potential after oral administration in mouse and rat at 2.0 mg/kg and rabbit at 0.09 mg/kg, or after s.c. (0.015 mg/kg, rat) and i.v. treatment (0.15 mg/kg, rabbit). In rats, increases in resorption rate were observed at oral dosage of > 0.015 mg/kg/day; however dependent on duration of dosing. Fertility in rats was not impaired up to 0.15 mg/kg. Doses up to 0.075 mg/kg did not affect the peri- and postnatal development of the progeny.

There was no mutagenic potential in the Ames test and micronucleus assay in mice. Clonidine was not tumorigenic in a carcinogenicity assay in rats.

No local irritating or sensitizing potential was found in guinea pigs and rabbits following i.v. and i.a. administrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose – microcrystalline
Starch – maize
Starch - pregelatinised maize
Lactose monohydrate
Talc – purified
Sodium starch glycollate Type A
Magnesium stearate (E470b)

The tablet formulation is colour-free, preservative-free, sugar-free, and does not contain gluten.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C. Keep out of reach of children.

6.5 Nature and contents of container

PVC/aluminium blister.

Each carton contains 112 tablets (4 blister strips of 28 tablets each).

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
20 December 2012

10. DATE OF REVISION OF THE TEXT

12 October 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	Product name change