

CLONIDINE TRANSDERMAL SYSTEM USP

1. Product Name

CLONIDINE TRANSDERMAL SYSTEM USP, 0.1 mg/day, 0.2 mg/day or 0.3 mg/day, transdermal patch.

2. Qualitative and Quantitative Composition

Each CLONIDINE TRANSDERMAL SYSTEM USP contains 0.1 mg/day, 0.2 mg/day or 0.3 mg/day of clonidine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

CLONIDINE TRANSDERMAL SYSTEM USP 0.1 mg/day: (2.52 mg/3.33 cm²). A rectangular patch with rounded corners consisting of a peach-coloured backing labelled with 'Mylan® Clonidine 0.1 mg/day' in brown ink, a solid matrix drug reservoir layer, an adhesive formulation layer, and an oversized removable release liner.

CLONIDINE TRANSDERMAL SYSTEM USP 0.2 mg/day: (5.04 mg/6.67 cm²). A rectangular patch with rounded corners consisting of a peach-coloured backing labelled with 'Mylan® Clonidine 0.2 mg/day' in brown ink, a solid matrix drug reservoir layer, an adhesive formulation layer, and an oversized removable release liner.

CLONIDINE TRANSDERMAL SYSTEM USP 0.3 mg/day: (7.56 mg/10.0 cm²). A rectangular patch with rounded corners consisting of a peach-coloured backing labelled with 'Mylan® Clonidine 0.3 mg/day' in brown ink, a solid matrix drug reservoir layer, an adhesive formulation layer, and an oversized removable release liner.

The rate of release of clonidine and content of clonidine in each system is given in the table below:

	Programmed Delivery <i>In vivo</i> / day Over 1 week	Clonidine content (mg)	Size (cm ²)
Clonidine Transdermal System USP, 0.1 mg/day	0.1 mg	2.52	3.33
Clonidine Transdermal System USP, 0.2 mg/day	0.2 mg	5.04	6.67
Clonidine Transdermal System USP, 0.3 mg/day	0.3 mg	7.56	10.0

4. Clinical Particulars

4.1 *Therapeutic indications*

CLONIDINE TRANSDERMAL SYSTEM USP is indicated for the treatment of mild to moderate hypertension. It can be used as monotherapy or concomitantly with other antihypertensive agents if required to enhance hypotensive effect.

4.2 *Dose and method of administration*

Dose

CLONIDINE TRANSDERMAL SYSTEM USP dosage should be titrated according to individual patient's therapeutic requirements. Patches should be inspected prior to use. Patches that are cut, divided, or damaged in any way should not be used. Commence with one CLONIDINE TRANSDERMAL SYSTEM USP 0.1 mg/day applied weekly.

If after one to two weeks the desired reduction in blood pressure is not achieved, increase the weekly dosage by changing to CLONIDINE TRANSDERMAL SYSTEM USP 0.2 mg/day. If this dosage is still not satisfactory after 1-2 weeks therapy then increase the weekly dosage by changing to CLONIDINE TRANSDERMAL SYSTEM USP 0.3 mg/day.

Most patients with mild to moderate hypertension will be controlled on one CLONIDINE TRANSDERMAL SYSTEM USP 0.3 mg/day or less. In more resistant cases where blood pressure is not satisfactorily controlled on one CLONIDINE TRANSDERMAL SYSTEM USP 0.3 mg/day, it is recommended that a diuretic and/or other antihypertensive agents be added to enhance the hypotensive effect. In this way, the dose of each individual drug may be reduced and side effects minimised. Higher doses of up to two CLONIDINE TRANSDERMAL SYSTEM USP 0.3 mg/day a week have been utilised. An increase in dosage above two CLONIDINE TRANSDERMAL SYSTEM USP 0.3 mg/day is usually not associated with additional efficacy.

When substituting CLONIDINE TRANSDERMAL SYSTEM USP in patients on prior oral antihypertensive therapy, including oral clonidine, physicians should be aware that the antihypertensive effect of CLONIDINE TRANSDERMAL SYSTEM USP might not commence until 2 – 3 days after initial application. Therefore, gradual reduction of prior drug dosage over 5 – 6 days is advised. Some or all previous antihypertensive treatment may have to be continued, particularly in patients with more severe forms of hypertension.

Special populations

Renal impairment

Dosage must be adjusted:

- according to the individual antihypertensive response which can show high variability in patients with renal insufficiency
- according to the degree of the renal impairment.

Careful monitoring is required. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

Method of administration

CLONIDINE TRANSDERMAL SYSTEM USP should be applied to a freshly cleaned, hairless area of the upper outer arm or chest. A new site should be used each week when applying new patches. If the system loosens during 7-day wearing, the adhesive cover should be applied directly over the system to ensure good adhesion. There have been rare reports of the need for patch changes prior to 7 days to maintain blood pressure control.

4.3 Contraindications

CLONIDINE TRANSDERMAL SYSTEM USP 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 block of 2nd or 3rd degree.

4.4 Special warnings and precautions for use

CLONIDINE TRANSDERMAL SYSTEM USP should be used with caution in patients with mild to moderate bradyarrhythmia such as low sinus rhythm, with disorders of cerebral or peripheral perfusion, depression, polyneuropathy, and constipation.

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

In hypertension caused by pheochromocytoma no therapeutic effect of CLONIDINE TRANSDERMAL SYSTEM USP can be expected.

Physicians considering starting CLONIDINE TRANSDERMAL SYSTEM USP therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 – 3 days after initial application of CLONIDINE TRANSDERMAL SYSTEM USP.

Clonidine, the active ingredient of CLONIDINE TRANSDERMAL SYSTEM USP, and its metabolites are extensively excreted with the urine. Renal insufficiency requires particularly careful adjustment of dosage (see section 4.2).

Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of CLONIDINE TRANSDERMAL SYSTEM USP after prolonged treatment with high doses, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headache or nausea have been reported. When discontinuing therapy with CLONIDINE TRANSDERMAL SYSTEM USP, the physician should reduce the dose gradually over 2 – 4 days.

An excessive rise in blood pressure following discontinuation of CLONIDINE TRANSDERMAL SYSTEM USP therapy can be reversed by administration of oral clonidine hydrochloride or by intravenous phentolamine or tolazoline (see section 4.5).

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.

In patients who have developed localised contact sensitisation to CLONIDINE TRANSDERMAL SYSTEM USP, substitution of oral clonidine therapy may in rare instances be associated with development of a generalised skin rash.

Patients should be instructed to consult their physicians promptly about the possible need to remove the patch if they observe moderate to severe localized erythema and/or vesicle formation at the site of application or generalized skin rash.

If a patient experiences isolated, mild localized skin irritation before completing 7 days of use, the system may be removed and replaced with a new system applied to a fresh skin site.

CLONIDINE TRANSDERMAL SYSTEM USP therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting CLONIDINE TRANSDERMAL SYSTEM USP therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of CLONIDINE TRANSDERMAL SYSTEM USP (see section 4.2).

CLONIDINE TRANSDERMAL SYSTEM USP should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may increase the risk of arcing, a phenomenon associated with the use of defibrillators.

Patients who wear contact lenses should be warned that treatment with CLONIDINE TRANSDERMAL SYSTEM USP may cause decreased lacrimation.

The use and the safety of clonidine in children and adolescents has little supporting evidence in randomized controlled trials and therefore cannot be recommended for use in this population.

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

The reduction in blood pressure induced by clonidine can be further potentiated by concurrent administration of other hypotensive agents. This can be of therapeutic use in the case of other antihypertensive agents such as diuretics, vasodilators, beta-receptor blockers, calcium antagonists and ACE-inhibitors, but not alpha₁-blocking agents.

Substances which raise blood pressure or induce a Na⁺ and water retaining effect such as non steroidal anti inflammatory agents can reduce the therapeutic effect of clonidine.

Substances with alpha₂-receptor blocking properties such as phentolamine or tolazoline may abolish the alpha₂-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 the 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.

The antihypertensive effect of clonidine may be reduced or abolished and orthostatic regulation disturbances may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

(Category B3)

There are limited amounts of data from the use of clonidine in pregnant women.

During pregnancy CLONIDINE TRANSDERMAL SYSTEM USP, as any drug, should only be administered if clearly needed. 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 the 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).

Post partum a transient rise in blood pressure in the newborn cannot be excluded.

Breast-feeding

Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. The use of CLONIDINE TRANSDERMAL SYSTEM USP during lactation is not recommended during breast feeding.

Fertility

No clinical studies on the effect on human fertility have been conducted with clonidine. Animal studies with clonidine did not indicate direct or indirect harmful effects with respect to the fertility index (see Section 5.3).

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 CLONIDINE TRANSDERMAL SYSTEM USP. 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.

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

Nervous system disorders: dizziness, sedation, headache, paraesthesia

Eye disorders: accommodation disorder, lacrimation decreased

Cardiac disorders: bradyarrhythmia, sinus bradycardia, atrioventricular block

Vascular disorders: orthostatic hypotension, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders: nasal dryness

Gastrointestinal disorders: dry mouth, constipation, nausea, salivary gland pain, vomiting, colonic pseudo-obstruction

Skin and subcutaneous tissue disorders: application site erythema, application site erosion, application site burn, application site discolouration, application site papules, application site dermatitis, urticaria, pruritus, rash, alopecia

Reproductive system and breast disorders: erectile dysfunction, gynecomastia

General disorders and administration site conditions: application site pain, 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. Manifestations of intoxication are due to generalised sympathetic depression and include pupillary constriction, lethargy, bradycardia, hypotension, hypothermia, somnolence including coma, respiratory depression including apnea. Paradoxical hypertension caused by stimulation of peripheral α_1 -receptors may occur.

Rare cases of CLONIDINE TRANSDERMAL SYSTEM USP poisoning due to accidental or deliberate mouthing or ingestion of the patch have been reported, most of them involving children.

Treatment

Careful monitoring and symptomatic measures. There is no specific antidote for clonidine overdose. If symptoms of poisoning occur following dermal exposure, remove all CLONIDINE TRANSDERMAL SYSTEM USP. After their removal, the plasma clonidine levels will persist for about 8 hours, then decline slowly over a period of several days.

In case of accidental overdose, symptomatic treatments and supportive care are suggested.

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiadrenergic agents, centrally acting, ATC code: C02AC01

Mechanism of action

Clonidine stimulates alpha-adrenoreceptors in the brain stem. This action results in reduced sympathetic outflow from the central nervous system and in decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact and therefore orthostatic symptoms are mild and infrequent.

During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal hemodynamic response to exercise.

Tolerance to the antihypertensive effect may develop in some patients, necessitating a re-evaluation of therapy.

5.2 Pharmacokinetic properties

Absorption

Clonidine is released from the CLONIDINE TRANSDERMAL SYSTEM USP transdermal patch at a relatively constant rate of $4.32 \pm 1.68 \mu\text{g/h}$ for 7 days. Steady-state clonidine plasma levels are obtained within three days after transdermal application to the upper outer arm and increase linearly with increasing size of the transdermal patch. Mean steady-state plasma concentrations with the 3.33 cm^2 , 6.67 cm^2 and 10.0 cm^2 systems are approx. 0.4 ng/ml , 0.8 ng/ml and 1.1 ng/ml , respectively. Comparable clonidine steady-state concentrations are reached after application to the

chest. Effective clonidine plasma concentrations are reached within 2 - 3 days after application of the first system. Steady-state clonidine plasma levels remain constant after removal of one system and application of a new system of the same size.

Kinetic parameters of clonidine were calculated from plasma concentrations after i.v. administration. The absolute bioavailability of clonidine from the CLONIDINE TRANSDERMAL SYSTEM USP dosage form is approximately 60%.

Distribution

The apparent volume of distribution (V_z) of clonidine is 197 L (2.9 L/kg). The drug crosses the blood-brain-barrier as well as the placenta-barrier. The plasma protein binding is 30-40%.

Biotransformation

Clonidine metabolites are mainly formed in the liver and pharmacologically inactive.

Elimination

Clonidine has a total clearance of 177 ml/min and a renal clearance of 102 ml/min. Plasma elimination half-life of clonidine determined after i.v. application is approximately 13 hours. After removal of the CLONIDINE TRANSDERMAL SYSTEM USP, clonidine plasma concentrations decline slowly with a half-life of approximately 20 hours, reflecting the slower absorption from the CLONIDINE TRANSDERMAL SYSTEM USP. Plasma elimination half-life can be prolonged in patients with severely impaired renal function up to 41 hours.

In an excretion balance study cumulative renal excretion (3-5 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 65% and total radioactivity excreted via the faeces was 22% after oral administration. Approximately 40-60% of the total radioactivity recovered in the urine within 24 hours accounts for the unchanged parent compound. The remainder of the urinary radioactivity consists of 5 clonidine metabolites, which are mainly formed in the liver and pharmacologically inactive.

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 approximative oral LD₅₀ values were 70 mg/kg (mouse), 190 mg/kg (rat), >15 mg/kg (dog) and 150 mg/kg in monkeys. Following subcutaneous injection, the LD₅₀ 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 oral repeat-dose toxicity studies clonidine was well tolerated at 0.1 mg/kg/day and 0.03 mg/kg/day (rat, 18 months and dog, 52 weeks, respectively). In a 52-week oral study in the monkey, the no observed adverse effect level (NOAEL) was 1.5 mg/kg/day. In a 13-week subcutaneous study in rats, the no adverse effect level (NOAEL) was 0.05 mg/kg/day. In intravenous studies, rabbits and dogs tolerated 0.01 mg/kg/day and 0.1 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 the mouse and the rat at 2.0 mg/kg/day and rabbit at 0.09 mg/kg/day, or after subcutaneous (0.016 mg/kg/day, rat) and i.v. treatment (0.15 mg/kg/day, rabbit). In rats, increases in resorption rate were observed at oral dosage of ≥ 0.015 mg/kg/day (equivalent to about 1/8 the oral MRHDD based on a mg/m² basis);

however dependent on duration of dosing. In rats, up to oral dosages of 0.15 mg/kg/day (about the oral MRHDD based on a mg/m² basis) fertility index and peri- and postnatal development of the progeny were not impaired.

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 intravenous and intra-articular administrations.

6. Pharmaceutical Particulars

6.1 *List of excipients*

CLONIDINE TRANSDERMAL SYSTEM USP also contains:

- mineral oil
- polyisobutylene
- colloidal silicon dioxide
- pigmented polyethylene/polyester film
- silicone/polyester film

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

2 years.

6.4 *Special precautions for storage*

Store at or below 25°C.

Store in a safe place out of reach of children.

6.5 *Nature and contents of container*

CLONIDINE TRANSDERMAL SYSTEM USP 0.1 mg/day; 0.2 mg/day and 0.3 mg/day are supplied in packs of 4 pouched systems with 4 adhesive covers per carton.

System structure and components

CLONIDINE TRANSDERMAL SYSTEM USP is a multi-layered film, 0.25 mm thick, containing clonidine as the active agent. System areas are 3.33 cm² (0.1 mg/day), 6.67 cm² (0.2 mg/day), and 10.0 cm² (0.3 mg/day) and the amount of drug released is directly proportional to area. The composition per unit area of all three dosages is identical.

Proceeding from the visible surface towards the surface attached to the skin are three consecutive layers:

1. a backing layer of pigmented polyethylene and polyester film;
2. a solid matrix reservoir of clonidine, mineral oil, polyisobutylene and colloidal silicon dioxide;
3. an adhesive formulation of clonidine, mineral oil, polyisobutylene and colloidal silicon dioxide.
Prior to use, a protective slit release liner of polyester that covers the adhesive formulation layer is removed.

CLONIDINE TRANSDERMAL SYSTEMS USP are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use.

Cross section of the system

(diagram not to scale)



6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

20 November 2014

10. Date of Revision of the Text

15 March 2022

Summary table of changes

Section	Summary of new information
All	Minor editorial changes Making section text “normal style” throughout document Other formatting changes to align with Viatris standard format Update sponsor name and logo

Section	Summary of new information
	<p>Addition of cross references for ease of use</p> <p>Minor updates for better flow, clarification and understanding</p> <p>Title added for Summary table of changes and column headings updated</p>
4.4	Addition of tolazoline injection to reverse excessive rise in blood pressure following discontinuation of clonidine
4.5	<p>Addition of information that if combined administration of clonidine and beta-receptor blockers are to be discontinued, the dose of the beta-receptor blocker must always be slowly diminished first followed by the clonidine.</p> <p>Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. Not recommended whilst breast feeding.</p>
4.6	Addition of medicine pregnancy category, limited data statement for use in pregnancy. Non-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity
4.9	Addition of statement "In case of accidental overdosage, symptomatic treatments and supportive care are suggested."
5.2	Elimination: addition of information on 5 clonidine metabolites being mainly formed in the liver and pharmacologically inactive.
5.3	<p>Toxicology: correction of tern from LD50 values to lethal dose ranges.</p> <p>Toxic trans-species signs of toxicity following exposure to clonidine. Addition of "At lethal doses, tonic-clonic convulsions occurred"</p>
6.1	<p>Updated into a list format</p> <p>Removal of gluten, lactose and sugar free statement as no data held to support this claim. No change in formulation.</p>
6.3	Conversion of shelf life from months to year format. No change in shelf life.
6.4	Storage updated to "Store at or below 25°C" to align fully to registered details. No change in storage condition.
6.5	System structure and components information moved from Pharmaceutical Form Section
8	Updated sponsor name and contact details

Section	Summary of new information
10	New date of "Date of Revision of the Text"