ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CATAPRESAN TTS-1 2.5 mg transdermal patches
CATAPRESAN TTS-2 5 mg transdermal patches
CATAPRESAN TTS-3 7.5 mg transdermal patches

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Catapresan TTS is a transdermal patch containing clonidine that allows continuous and constant systemic delivery of the active substance for 7 days.
Clonidine is an imidazole derivative whose chemical name is 2,6-dichloro-N-2-imidazolidinylidenebenzenamine.

CATAPRESAN TTS-1 2.5 mg transdermal patches (surface area of 3.5 cm^2)
Programmed for *in vivo* delivery of 0.1 mg of clonidine a day for 7 days, contains:
Active substance: clonidine 2.5 mg

CATAPRESAN TTS-1 2.5 mg transdermal patches (surface area of 7.0 cm^2)
Programmed for *in vivo* delivery of 0.2 mg of clonidine a day for 7 days, contains:
Active substance: clonidine 5 mg

CATAPRESAN TTS-3 7.5 mg transdermal patches (surface area of 10.5 cm^2)
Programmed for *in vivo* delivery of 0.3 mg of clonidine a day for 7 days, contains:
Active substance: clonidine 7.5 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patches
Rectangular patches with rounded corners; the adhesive side is opaque white, covered with two overlapping transparent protective liners; the non-adhesive side is light brown with a diagonal print showing the name of the active substance followed by TTS-1 or TTS-2 or TTS-3 and the company logo.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Catapresan TTS is indicated in the treatment of all forms of arterial hypertension. Catapresan TTS can be used as monotherapy or in combination with other antihypertensive agents.

4.2 Posology and method of administration

Posology

Treatment with Catapresan TTS should be “adjusted” according to individual therapeutic needs, should commence with Catapresan TTS-1 2.5 mg transdermal patches.
If after 1 or 2 weeks the reduction in blood pressure is insufficient, the dose can be increased by adding another 2.5 mg patch or by using Catapresan TTS-2 5 mg transdermal patch.

A dosage increase exceeding two Catapresan TTS 7.5 mg patches is not usually accompanied by an increase in efficacy.

When Catapresan TTS is applied for the first time as replacement for oral therapy with clonidine hydrochloride or other antihypertensive medicinal products, the physician must be aware that the antihypertensive effect exerted by Catapresan TTS transdermal patch may not be achieved before 2-3 days. Therefore, it is advisable to gradually reduce the dosage of the medicinal product in use; some or all of the previous antihypertensive treatments can be maintained, especially in patients with more severe forms of hypertension.

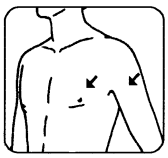
Renal impairment
The dose must be adjusted according to both the individual response, which can vary greatly in patients with renal impairment, and the degree of renal impairment.
Continuous monitoring is necessary. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to administer additional doses of clonidine after dialysis.

Paediatric population
There is insufficient evidence available to support the use of clonidine in children and adolescents under 18 years of age. The use of clonidine is therefore not recommended in paediatric subjects under 18 years of age.

Method of administration
The Catapresan TTS transdermal system must be applied to an area of intact, hairless skin on the upper chest or outer upper arm, once every 7 days. Each new Catapresan TTS patch must be applied to a different area of skin from that of the previous patch. Before application, remove the transparent film protecting the adhesive layer of the system. If the TTS transdermal system starts to loosen during the 7 days of application, the adhesive patch cover should be applied directly onto the system itself to ensure good adhesion. There have been rare reports of the need for patch changes prior to 7 days to keep the blood pressure under control.

1) Apply one Catapresan TTS transdermal patch every 7 days, on the same day of the week.

2) Choose an application area that is hairless (for example the outer arm or upper chest) (fig. 1).

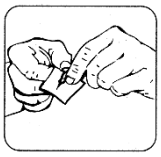
Fig. 1 

The chosen area must be free of cuts, abrasions, irritations, encrustations and scars and must be perfectly dry before the Catapresan TTS transdermal patch is applied.
It is advisable not to apply Catapresan TTS transdermal patch in the folds of the skin or in sites where it could be constricted by clothing, to avoid premature detachment of the patch itself.

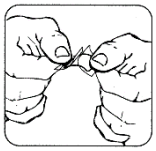
3) Wash your hands and dry them thoroughly before removing the transdermal system from the packaging.

4) Wash the chosen area only with soap and water and dry it carefully.

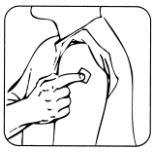
5) Open the sachet labelled “Catapresan TTS (clonidine)” (fig. 2) and remove the transdermal patch.

Fig. 2 

6) Remove the two parts of the transparent film by peeling them away from the center of the patch without touching the medicated surface with your hands (fig. 3).

Fig. 3 

7) Apply the Catapresan TTS transdermal patch to the chosen area of skin by applying light pressure around the edges (fig. 4).
Wash hands immediately after application.

Fig. 4 

8) After 7 days, remove the old patch and apply a new one to a different area of skin, repeating the procedure from point 2 onwards.

Using the overlay patch

Attention: the adhesive overlay patch does not contain any medicinal product and should not be used alone.

The adhesive overlay patch should be applied directly on top of the Catapresan TTS transdermal patch only if the patch starts detaching from the skin.

1) Wash your hands with soap and water and dry them thoroughly.

2) Use a dry cloth to wipe the area where the Catapresan TTS transdermal patch is applied and by exerting light pressure make sure that the edges of the Catapresan TTS transdermal patch are in contact with the skin.

3) Open the sachet labelled "Adhesive overlay patch" and remove the protective plastic film.

4) Apply the adhesive overlay patch by pressing gently, especially around the edges, directly on top of the Catapresan TTS transdermal patch taking care to position the adhesive overlay patch centrally over the Catapresan TTS transdermal patch (fig.5).

Fig. 5 

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in paragraph 6.1.

Catapresan TTS must not be used in patients with proven hypersensitivity to the active substance or to any other component of the transdermal patch and in patients with severe bradyarrhythmia, resulting from sinus node disease or second or third degree atrioventricular block.

4.4 Special warnings and precautions for use

Catapresan TTS should be used with caution in patients with mild to moderate bradyarrhythmia such as low sinus rhythm, with Raynaud syndrome and other peripheral or cerebral perfusion disorders, depression, polyneuropathy and constipation.
In case of hypertension caused by pheochromocytoma, the use of Catapresan TTS has not shown any therapeutic effect.
Clonidine, the active substance of Catapresan TTS, and its metabolites are primarily excreted by the kidneys. Particularly careful titration is required in patients with renal impairment (see section 4.2).
Patients with heart failure or severe coronary artery disease should be particularly closely monitored during treatment with Catapresan TTS, as with other antihypertensive agents.

Patients should be advised not to discontinue therapy without consulting their doctor. Sudden discontinuation of prolonged treatment with Catapresan TTS at high doses has induced restlessness, palpitations, rapid increase in blood pressure, agitation, tremors, headache, or nausea. If therapy with Catapresan TTS is to be discontinued, the doctor should taper the dose gradually over 2 - 4 days.

An excessive increase in blood pressure following discontinuation of treatment with Catapresan TTS can be reversed by administering clonidine hydrochloride orally or phentolamine intravenously (see section 4.5).

If combined treatment with a beta-blocker requires discontinuation of the antihypertensive therapy, the beta-blocker first and then the clonidine must be gradually withdrawn.

In patients who have developed localised skin reaction to Catapresan TTS, the switch to oral clonidine may be associated with the development of generalised skin rash.

Patients should be instructed to consult their physician promptly regarding the possible need to remove the patch if they develop moderate to severe localised erythema and/or blistering in the patch application site, or generalised rash.

If a patient develops local, isolated and mild skin irritation within 7 days of patch application, it can be removed and replaced with a new one, applied onto another skin area.

Catapresan TTS should not be discontinued during the operative period. Blood pressure should be closely monitored during surgery and additional measures to control blood pressure should be available if needed.
When considering initiation of treatment with Catapresan TTS during the perioperative period, it should be considered that therapeutic plasma clonidine levels are not achieved until 2 – 3 days after the initial application of Catapresan TTS (see section 4.2).

Catapresan TTS should be removed before defibrillation or cardioversion procedures due to the potential changes in electrical conductivity, which may increase the risk of arcing, a phenomenon associated with the use of defibrillators. As Catapresan TTS contains aluminium, it is recommended to be removed before the patient undergoes an MRI. Skin burns at the patch application site have been reported in a number of patients wearing a transdermal patch containing aluminium during MRI scans.

Patients who use contact lenses should be warned that treatment with Catapresan TTS may cause decreased lacrimation.
The use and safety of clonidine in children and adolescents has not been confirmed in randomized controlled studies; therefore use in this patient population cannot be recommended.

In particular, when clonidine is used off-label in combination with methylphenidate in children with ADHD (attention deficit hyperactivity disorder), severe adverse reactions including death have been observed. Therefore, the use of clonidine in this combination is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

The antihypertensive effect of Catapresan TTS may be enhanced by concomitant administration of other drugs used to lower blood pressure. This can be used therapeutically by administering other types of antihypertensives such as diuretics, vasodilators, beta blockers, calcium channel blockers and ACE inhibitors, but not alpha-1 blockers.

Substances which raise blood pressure or induce sodium ion and water retention, such as nonsteroidal anti-inflammatory drugs, may reduce the efficacy of clonidine.

Substances with α_2-blocking efficacy, such as phentolamine or tolazoline, may diminish the alpha-$_2$ receptor-mediated effects of clonidine in a dose-dependent manner.
Concomitant administration of substances with negative chronotropic or dromotropic activity such as beta blockers or digitalis glycosides may cause or exacerbate rhythm disorders in patients with bradycardia.

It cannot be ruled out that concomitant administration of a beta blocker may cause or exacerbate peripheral vascular disease.

The antihypertensive effect of clonidine may be reduced or outweighed and changes in orthostatic regulation can be induced or aggravated by concomitant administration of tricyclic antidepressants or neuroleptic agents with alpha-blocking activity.

The effects of CNS-inhibiting substances, or the effects of alcohol, may be enhanced by clonidine

4.6 Fertility, pregnancy and lactation

Pregnancy
Not appropriate and controlled studies have been conducted in pregnant women.
Like all other medicinal products, Catapresan TTS should only be administered during pregnancy when absolutely necessary. In this case, close monitoring of the mother and the baby is recommended.
Clonidine crosses the placental barrier and may slow the foetus' heart rate.
There is no adequate experience regarding the long-term effects of prenatal exposure to the medicinal product. Oral forms of clonidine should be preferred during pregnancy.
Intravenous administration of clonidine should be avoided.
Preclinical studies conducted with clonidine in rats and rabbits did not show any teratogenic effects. In rats, increased reabsorption rates were observed following oral administration of clonidine (see section 5.3).
Post-partum, a transient increase in blood pressure in the newborn cannot be excluded.

Breast-feeding
Due to the lack of supporting data, the use of Catapresan TTS during breastfeeding is not recommended.

Fertility
No clinical studies have been conducted on the effects of clonidine on human fertility.
Animal studies with clonidine have shown no direct or indirect harmful effects with respect to the fertility indices.

4.7 Effects on ability to drive and use machines

No studies have been conducted to evaluate the effects on the ability to drive and use machines. However, during treatment with Catapresan TTS, patients must be warned of the possible undesirable effects that may occur, such as: dizziness, sedation and accommodation disorders. Therefore, particular caution should be recommended when driving vehicles or using machines. If patients experience any of the above undesirable effects, potentially hazardous activities, such as driving or using machines, should be avoided.

4.8 Undesirable effects

Most of the undesirable effects experienced during treatment with Catapresan TTS were mild and tended to decrease during treatment. The undesirable effects are listed below by system organ class and frequency, according to the following categories:
Very common ≥ 1/10
Common ≥ 1/100 < 1/10
Uncommon ≥ 1/1,000 < 1/100
Rare ≥ 1/10,000 < 1/1,000
Very rare < 1/10,000
Not known, frequency cannot be estimated from the available data.

Psychiatric disorders:
Common: Depression, sleep disorders.
Uncommon: Confusional state, delusional perception, hallucinations, decreased libido, nightmares.

Nervous system disorders:
Very common: Dizziness, sedation.
Common: Headache, drowsiness.
Uncommon: Paraesthesia.

Eye disorders:
Uncommon: Accommodation disorders.
Rare: Reduced lacrimation.

Cardiac disorders:
Uncommon: Bradyarrhythmia, sinus bradycardia.
Rare: Atrioventricular block.

Vascular disorders:
Very common: Postural hypotension.
Uncommon: Raynaud syndrome.

Respiratory, thoracic and mediastinal disorders:
Rare: Dryness of the nasal mucosae.

Gastrointestinal disorders:
Very common: Dry mouth.
Common: Constipation, nausea, salivary gland pain, vomiting.
Rare: Pseudo-obstructions of the colon.

Skin and subcutaneous tissue disorders:
Very common: Application site erythema.
Common: Application site irritation, application site burn, application site discoloration.
Uncommon: Application site papules, application site dermatitis, urticaria, pruritus, rash.
Rare: Alopecia.

Reproductive system and breast disorders:
Common: Erectile dysfunction.
Rare: Gynecomastia.

General disorders and administration site conditions:
Common: Application site pain, fatigue.
Uncommon: Malaise.

Diagnostic test abnormalities:
Rare: Glycaemia elevation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important, as it allows continuous monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system at https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

4.9 Overdose

Symptoms
Clonidine has a wide therapeutic range. Clonidine intoxication presents with general sympathetic nervous system depression, which may cause constriction of the pupils, lethargy, bradycardia, hypotension, hypothermia, drowsiness through to coma, respiratory depression including apnoea. Paradoxical hypertension may ensue following peripheral α1 receptor stimulation.

Rare cases of Catapresan TTS poisoning have been reported following accidental or intentional ingestion of patches. Most of these cases involved children.

Treatment
Close monitoring and symptomatic measures.
There is no specific antidote for clonidine overdose. If symptoms of overdose occur following cutaneous application of a patch, all transdermal patches must be removed. After removal of the patch, plasma levels of clonidine are maintained for approximately 8 hours, then slowly decline over a period of several days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Imidazoline receptor agonists, ATC code: C02AC01.

Clonidine stimulates the alpha-adrenergic receptors in the brainstem, causing a reduction in sympathetic outflow and consequent reduction 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 not affected and therefore the postural effects are mild and uncommon. During long-term therapy with clonidine, cardiac output tends to normalise, whereas peripheral resistance remains low. A decrease in heart rate has been observed in the majority of patients treated with clonidine; however, the medicinal product does not affect the normal haemodynamic response to exercise.
Some patients may develop tolerance of the antihypertensive effect of clonidine; in these cases, the treatment must be reviewed.

The efficacy of clonidine in the treatment of hypertension has been evaluated in 5 clinical studies on paediatric populations.
The efficacy data confirm the properties of clonidine in reducing systolic and diastolic blood pressure.

However, due to limited data and methodological shortcomings, definitive conclusions cannot be drawn on the use of clonidine in hypertensive children.
The efficacy of clonidine has also been evaluated in certain clinical studies in paediatric patients with ADHD, Tourette syndrome and stuttering. The efficacy of clonidine in these situations has not been demonstrated.
Clonidine was not shown to be efficacious in two small paediatric studies in the treatment of migraine.
In paediatric clinical studies, the most common undesirable effects were drowsiness, dry mouth, headache, dizziness and insomnia. These undesirable effects can have a serious impact on children's everyday activities.
Overall, the safety and efficacy of clonidine in children and adolescents have not been established (see section 4.2).

5.2 Pharmacokinetic properties

Clonidine is delivered by Catapresan TTS at a relatively constant rate of 4.32 ± 1.68 µg/h over 7 days. Steady-state clonidine plasma levels are obtained three days after application of the patch onto the outer upper arm and increase linearly with increasing size of the patch. Using 3.5 cm², 7.0 cm² and 10.5 cm² patches, the mean steady-state plasma concentrations are approximately 0.4 ng/mL, 0.8 ng/mL and 1.1 ng/mL, respectively. Similar steady-state concentrations are obtained when the patch is applied onto the chest. Efficacious plasma concentrations of clonidine are obtained 2-3 days after application of the first patch. Steady-state blood clonidine concentrations remain unchanged after removal of a patch and application of another patch of the same size.
The kinetic parameters of clonidine were calculated on the basis of plasma concentrations following intravenous administration. The absolute bioavailability of the clonidine delivered by a Catapresan TTS patch is approximately 60%.
The apparent volume of distribution (Vz) of clonidine is 197 L (2.9 L/Kg). The drug crosses both the blood-brain barrier and the placental barrier. It has a plasma protein binding affinity of 30 - 40%.
Clonidine has a total clearance of 177 mL/min and a renal clearance of 102 mL/min.
The plasma elimination half-life of clonidine following intravenous administration is approximately 13 hours. After removal of the patch, plasma concentrations of clonidine decline slowly with a half-life of approximately 20 hours, indicating a slower absorption of clonidine released from Catapresan TTS. In patients with severe renal impairment, the blood elimination half-life may increase up to 41 hours.
In a study on the excretion balance, the cumulative renal excretion (3-5 days) of the radioactive labels bound to the active substance (original compound and all metabolites) represented 65% and the total radioactivity excreted in stools, following oral administration, was 22%.
Approximately 40-60% of the total radioactivity recovered in the urine over 24 hours can be attributed to the unchanged parent compound. The remainder of the urinary radioactivity consists of 5 clonidine metabolites, which are mainly formed in the liver and which are pharmacologically inactive.

5.3 Preclinical safety data

Single-dose toxicity studies with clonidine have shown oral LD50 values of between approximately > 15 mg/kg (dogs), and 150 mg/kg (monkeys). Following subcutaneous administration, the LD50 values were > 3 mg/kg in dogs and 153 mg/kg in rats. Following intravenous administration, the LD50 values were between 6 mg/kg (dogs) and < 21 mg/kg (rats).
Following administration of the drug, regardless of the route of administration used, the signs of toxicity observed were exophthalmos, ataxia and tremors. Excitation and aggressiveness alternating with sedation (mice, rats, dogs), salivation and tachypnoea (dogs), hypothermia and apathy (monkeys) were also observed.

In repeated oral dose toxicity studies (lasting 18 months in rats and 52 weeks in dogs), clonidine was well tolerated at oral doses of 0.1 mg/kg/day (rats) and 0.03 mg/kg/day (dogs). In a 52-week study in monkeys, the no-observed-adverse-effect-level (NOAEL) following oral administration was 1.5 mg/kg/day. In a 13-week study in rats, the NOAEL following subcutaneous administration was 0.05 mg/kg/day.

In studies using intravenous administration, rabbits and dogs tolerated doses of 0.01 mg/kg/day and 0.1 mg/kg/day of clonidine for 5 and 4 weeks, respectively.
Higher doses caused hyperactivity, aggressiveness, decreased food intake and weight gain (rats), sedation (rabbits) or cardio- and hepatomegaly with increased plasma concentrations of GPT, alkaline phosphatase and alpha-globulins and focal liver necrosis (dogs).

No teratogenic potential was observed following oral administration of 2.0 mg/kg/day in mice and rats and 0.09 mg/kg/day in rabbits or following subcutaneous administration (of 0.016 mg/kg/day in rats) and following intravenous administration (of 0.15 mg/kg in rabbits).

In rats, increases in resorption rate were seen at oral doses of ≥ 0.015 mg/kg/day (equivalent to approximately 1/8 of the maximum recommended human daily dose (MRHDD) based on a mg/m^2 basis), depending on treatment duration.
In rats, oral doses of up to 0.15 mg/kg/day (roughly equivalent to the maximum recommended human daily dose based on mg/m^2 basis) did not affect the fertility index and the peri- and postnatal development of the offspring.
The Ames and micronucleus tests in mice did not yield any evidence of mutagenic potential. In a carcinogenicity study in rats, clonidine was not found to be carcinogenic.
Intravenous and intra-arterial administration in guinea pigs and rabbits did not suggest any tendency to cause local irritation or sensitisation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CATAPRESAN TTS-1 2.5 mg transdermal patches (surface area of 3.5 cm^2)
Excipients and vehicle:
light mineral oil; high molecular weight polyisobutylene; medium molecular weight polyisobutylene; silicon dioxide colloidal.
Film constituents:
polyethylene medium density, aluminium-polyester/ethylene vinyl acetate copolymer; polypropylene film; fluorocarbon diacrylate-coated/polyester film.

CATAPRESAN TTS-2 5 mg transdermal patches (surface area of 7.0 cm^2)
Excipients and vehicle:
light mineral oil; high molecular weight polyisobutylene; medium molecular weight polyisobutylene; silicon dioxide colloidal.
Film constituents:
polyethylene medium density, aluminium-polyester/ethylene vinyl acetate copolymer; polypropylene film; fluorocarbon diacrylate-coated/polyester film.

CATAPRESAN TTS-3 7.5 mg transdermal patches (surface area of 10.5 cm^2)
Excipients and vehicle:
light mineral oil; high molecular weight polyisobutylene; medium molecular weight polyisobutylene; silicon dioxide colloidal.
Film constituents:
polyethylene medium density, aluminium-polyester/ethylene vinyl acetate copolymer; polypropylene film; fluorocarbon diacrylate-coated/polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Sachet containing the therapeutic transdermal patch consisting of paper/polyethylene/aluminium foil/ low-density polyethylene–linear low-density polyethylene.
Sachet containing adhesive patch cover consisting of paper/low-density polyethylene/aluminium foil/ low-density polyethylene.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lavipharm S.A.
Agias Marinas street,
19002 Peania, Attica, Greece

8. MARKETING AUTHORISATION NUMBER(S)

CATAPRESAN TTS-1 2.5 mg transdermal patches: MA no. 027393014
CATAPRESAN TTS-2 5 mg transdermal patches: MA no. 027393026
CATAPRESAN TTS-3 7.5 mg transdermal patches: MA no. 027393038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/01/1993
Date of latest renewal: 01/02/2008

10. DATE OF REVISION OF THE TEXT

November 2023