SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Coracten SR capsules 10 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg nifedipine.

Excipients with known effect: sucrose and lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard

Opaque brownish-pink cap and opaque grey body, printed in white with ‘Coracten’ on the body and ‘10 mg’ on the cap, containing yellow spherical granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Coracten SR capsules are indicated in adults for the prophylaxis of chronic stable angina pectoris and the treatment of hypertension.

They are also indicated for the treatment of Prinzmetal (variant) angina when diagnosed by a cardiologist.

4.2 Posology and method of administration

Posology

The recommended starting dose of Coracten SR capsules is 10mg every 12 hours swallowed with water with subsequent titration of dosage according to response. The dose may be adjusted to 40mg every 12 hours.

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (see section 4.5).

Duration of treatment
Treatment may be continued indefinitely.

Elderly (≥ 65 years)
The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required.

Hepatic impairment
Caution should be exercised in treating patients with hepatic impairment. In these patients the use of one 10mg Coracten SR capsule every 12 hours, together with careful monitoring, is suggested when commencing therapy.

Renal impairment
Dosage adjustments are not usually required in patients with renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of Coracten SR capsules in children below 18 years of age has not been established. Currently available data for the use of nifedipine in hypertension are described in section 5.1.

Method of administration

Oral use.

Coracten SR capsules should not be taken with grapefruit juice (see section 4.5).

4.3 Contraindications

Coracten SR capsules are contra-indicated in patients with known hypersensitivity to nifedipine or other dihydropyridines because of the theoretical risk of cross reactivity. They should also not be used in cases of known hypersensitivity to any of the excipients listed in section 4.4 and 6.1.

They should not be used in women who are or who may become pregnant (see section 4.6).

Coracten SR capsules should not be used in clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction. They should not be used in patients in cardiogenic shock.

Coracten SR capsules should not be used for the treatment of acute attacks of angina, or in patients who have had ischaemic pain following its administration previously.

The safety of Coracten SR capsules in malignant hypertension has not been established.

Coracten SR capsules should not be used for secondary prevention of myocardial infarction.

Coracten SR capsules are contra-indicated in patients with acute porphyria.

Coracten SR capsules should not be used in patients with Kock pouch (ileosetomy after proctocolectomy).

Coracten SR capsules should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see section 4.5).

4.4 Special warnings and precautions for use

Nifedipine should be used with caution in patients who are hypotensive (severe hypotension with systolic blood pressure less than 90 mm Hg).

Nifedipine should be used with caution in patients whose cardiac reserve is poor; in patients with heart failure or significantly impaired left ventricular function. Deterioration of heart failure has occasionally been observed with nifedipine.

The use of Nifedipine in diabetic patients may require adjustment of their diabetic therapy.

In dialysis patients with malignant hypertension and irreversible renal failure with hypovolaemia, a significant drop in blood pressure may occur due to the vasodilator effects of nifedipine.

Excessive falls in blood pressure may result in transient blindness. If affected the patient should not attempt to drive or use machinery (see section 4.8).

Although a ‘steal’ effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

Nifedipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt withdrawal of beta-blocking drugs. Withdrawal of any previously prescribed beta-blockers should be gradual, preferably over 8 to 10 days.

Nifedipine may be used in combination with beta-blockers and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension and/or cardiac failure must be borne in mind. Nifedipine will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Coracten SR capsules is not recommended for use during breast-feeding because nifedipine has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known (see section 4.6).

In patients with impaired liver function, careful monitoring, and in severe cases, a dose reduction may be necessary.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see section 4.5).

Drugs, which are inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine are, e.g.:

- macrolide antibiotics (e.g. erythromycin)
- anti-HIV protease inhibitors (e.g. ritonavir)
- azole antimycotics (e.g. ketoconazole)
- the antidepressants nefazodone and fluoxetine
- quinupristin/dalfopristin
- valproic acid
- cimetidine.

Upon co-administration with these drugs, the blood pressure should be monitored and if necessary, a reduction of the nifedipine dose should be considered (see section 4.5).

This medicinal product contains sucrose and lactose monohydrate. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, total lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

For use in special populations see section 4.2.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine (see section 4.4).

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated (see section 4.3).

Upon co-administration of known inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see sections 4.2 and 4.4). In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.

Drugs increasing nifedipine exposure:
• *macrolide antibiotics (e.g., erythromycin)*
• *anti-HIV protease inhibitors (e.g., ritonavir)*
• *azole anti-mycotics (e.g., ketoconazole)*
• *fluoxetine*
• *nefazodone*
• *quinupristin/dalfopristin*
• *cisapride*
• *valproic acid*
• *cimetidine*
• *diltiazem*

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to nifedipine should be monitored and, if necessary, an increase in the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

Increased plasma levels of nifedipine have been reported during concomitant use of alcohol, cyclosporin, gingko biloba and ginseng.

Enhanced hypotensive effect of nifedipine may occur with: aldesleukin, alprostadil, anaesthetics, antipsychotics, diuretics, phenothiazides, prazosin and intravenous ionic X-ray contrast medium. Profound hypotension has been reported with nifedipine and intravenous magnesium sulphate in the treatment of pre-eclampsia

Drugs decreasing nifedipine exposure:
- *rifampicin (see above)*
- *phenytoin*
- *carbamazepine*
- *phenobarbital*

Decreased plasma levels of nifedipine have also been reported during concomitant use of St John's Wort.

Effects of nifedipine on other drugs

Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives.

When nifedipine is administered simultaneously with beta-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

Digoxin: The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be subjected to precautionary checks for symptoms of digoxin overdosage and, if necessary, the glycoside dose should be reduced.

Quinidine: Co-administration of nifedipine with quinidine may lower plasma quinidine levels, and after discontinuation of nifedipine, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

Tacrolimus: Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

The plasma concentrations of phenytoin, theophylline, non-depolarising muscle relaxants (e.g. tubocurarine) are increased when used in combination with nifedipine.

There is an increased risk of excessive hypotension, bradycardia and heart failure with β-blockers.

Nifedipine may result in increased levels of mizolastine due to inhibition of cytochrome CYP3A4.

Nifedipine may increase the neuromuscular blocking effects of vecuronium.

Drug food interactions

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice. Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine (see section 4.2).

Other forms of interaction

Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid falsely. However, HPLC measurements are unaffected.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Because animal studies show embryotoxicity and teratogenicity, Coracten SR capsules are contra-indicated during pregnancy (see section 4.3). Embryotoxicity was noted at 6 to 20 times the maximum recommended dose for Coracten SR capsules given to rats, mice and rabbits, and teratogenicity was noted in rabbits given 20 times the maximum recommended dose for Coracten SR capsules. There are no adequate and well-controlled studies in pregnant women.

An increase in perinatal asphyxia, caesarean delivery as well as prematurity and intrauterine growth retardation has been reported, however it is unclear whether these reports are due to the underlying hypertension, its treatment or to a specific drug effect.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as a tocolytic agent during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.

Breast-feeding

Nifedipine is excreted in breast milk, therefore Coracten SR capsules are not recommended during lactation (see section 4.4).

Fertility

In single cases of *in-vitro* fertilization calcium-antagonists like nifedipine have been associated with reversible biochemical change in the spermatozoa's head section that may result in impaired sperm function. Nifedipine should be considered as a possible cause if there is no other explanation for unsuccessful fathering.

4.7 Effects on ability to drive and use machines

Reactions to the drug, which vary in intensity from individual to individual, may impair the ability to drive or to operate machinery (see section 4.8). This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

Dizziness and lethargy are potential undesirable effects. If affected do not attempt to drive or use machinery (see section 4.8).

Excessive falls in blood pressure may result in transient blindness. If affected do not attempt to drive or use machinery (see section 4.8).

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below: ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%). Most side-effects are consequences of the vasodilatory effects of nifedipine.

The frequencies of ADRs reported with nifedipine containing products are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). The ADRs identified only during the ongoing postmarketing surveillance and for which a frequency could not be estimated, are listed under "Not known".

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				Agranulocytosis Leukopenia
Immune system disorders		Allergic reaction Allergic oedema / angioedema (incl. larynx oedema [1])	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction Systemic allergic reactions
Psychiatric disorders		Anxiety reactions Sleep disorders	Mood changes	Depression
Metabolism and nutrition disorders				Hyperglycaemia

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Nervous system disorders	Headache	Vertigo Migraine Dizziness Tremor	Par-/ Dysaesthesia	Hypoaesthesia Somnolence Lethargy Cerebral ischemia (due to excessive fall in blood pressure)
Eye disorders		Visual disturbances		Eye pain Transient blindness (due to excessive fall in blood pressure)
Cardiac disorders		Tachycardia Palpitations		Chest pain (Angina Pectoris) Myocardial infarction[2] Myocardial ischemia (due to excessive fall in blood pressure)
Vascular disorders	Oedema (incl. peripheral oedema) Vasodilatation	Hypotension Syncope		Flushing

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Respiratory, thoracic, and mediastinal disorders		Nosebleed Nasal congestion		Dyspnea Pulmonary oedema*
Gastrointestinal disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Vomiting Gastrooesophageal sphincter insufficiency Diarrhoea
Hepatobiliary disorders		Transient increase in liver enzymes		Jaundice Intra-hepatic cholestasis
Skin and subcutaneous tissue disorders		Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura Telangiectasia Erythema multiforme Pemphigoid reaction Exfoliative dermatitis Purpura
Musculoskeletal and connective		Muscle cramps Joint		Arthralgia Myalgia Worsenin

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
tissue disorders		swelling		g of myasthenia gravis
Renal and urinary disorders		Polyuria Dysuria		Increased frequency of micturition
Reproductive system and breast disorders		Erectile dysfunction		Gynaecomastia (long-term therapy)
General disorders and administration site conditions	Feeling unwell	Unspecific pain Chills		Fever

[1] = may result in life-threatening outcome.
[2] = The occurrence of myocardial infarction has been described although it is not possible to distinguish such an event from the natural course of ischaemic heart disease.
*cases have been reported when used as tocolytic during pregnancy (see section 4.6)

In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

Reporting of Suspected Adverse Reactions
Reporting suspected adverse after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms
Reports of nifedipine overdosage are limited and symptoms are not necessarily dose-related. Severe hypotension due to vasodilation, and tachycardia or bradycardia are the most likely manifestations of overdose.

Metabolic disturbances include hyperglycaemia, metabolic acidosis and hypo- or hyperkalaemia.

Cardiac effects may include heart block, AV dissociation and asystole, and cardiogenic shock with pulmonary oedema.

Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, hypoxia, unconsciousness and coma.

Treatment

As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority.

After oral ingestion, gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

Elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

The benefit of gastric decontamination is uncertain.

1. Consider activated charcoal (50 g for adults, 1 g/kg for children) if the patient presents within 1 hour of ingestion of a potentially toxic amount.

Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for sustained release (SR, MR) preparations there is no evidence to support this.

2. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.

3. Consider further doses of activated charcoal every 4 hours if a clinically significant amount of a sustained release preparation has been ingested with a single dose of an osmotic laxative (e.g. sorbitol, lactulose or magnesium sulfate).

4. Asymptomatic patients should be observed for at least 4 hours after ingestion and for 12 hours if a sustained release preparation has been taken.

Haemodialysis serves no purpose, as nifedipine is not dialyzable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Blood pressure, ECG, central arterial pressure, pulmonary wedge pressure, urea and electrolytes should be monitored.

Hypotension as a result of cardiogenic shock and arterial vasodilation should be treated with elevation of the feet and plasma expanders. If these measures are ineffective, hypotension may be treated with 10% calcium gluconate 10-20 ml intravenously over 5-10 minutes. If the effects are inadequate, the treatment can be continued, with ECG monitoring. In addition, beta-sympathomimetics may be given, e.g. isoprenaline 0.2 mg slowly i.v. or as a

continuous infusion of 5µg/min. If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required.

Additional fluids should be administered with caution to avoid cardiac overload.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives, ATC code: C08CA05

Nifedipine is a specific and potent calcium antagonist of the 1, 4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.

In hypertension, the main action of Coracten SR capsules is to cause peripheral vasodilatation and thus reduce peripheral resistance.

In angina, Coracten SR capsules reduces peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume, whilst decreasing after-load.

Additionally, nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.
Nifedipine reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

Coracten SR capsules administered twice-daily provides 24-hour control of raised blood pressure. Coracten SR capsules causes reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, Coracten SR capsules has little or no effect on blood pressure.

<u>Paediatric population</u>
Limited information on comparison of nifedipine with other antihypertensives is available for both acute hypertension and long-term hypertension with

different formulations in different dosages. Antihypertensive effects of nifedipine have been demonstrated but dose recommendations, long term safety and effect on cardiovascular outcome remain unestablished. Paediatric dosing forms are lacking.

5.2 Pharmacokinetic properties

Coracten SR Capsules are a sustained release formulation of nifedipine designed to provide less fluctuation and more prolonged nifedipine blood concentrations than standard immediate release preparations.

Nifedipine is highly protein bound. It undergoes hepatic oxidation to inactive metabolites which are excreted in the urine (80%) and faeces (20%).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproduction toxicology
Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs.
Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period.

Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). The risk to humans cannot be ruled out if a sufficiently high systemic exposure is achieved, however, all of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and were several times the recommended maximum dose for humans (see Section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Sucrose,

Maize Starch
Lactose Monohydrate
Povidone K30
Methacrylic acid copolymer type A (Eudragit L100)
Talc
Purified Water

Capsule shells:
Gelatin
Red iron oxide (E172)
Yellow iron oxide (E172)
Black iron oxide (E172)
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in original pack at a temperature not exceeding 30°C and protect from light.

6.5 Nature and contents of container

Coracten SR capsules are presented in blister strips packed in cartons containing 10, 15, 30, 56, 60, 100, 150, 250, 500 and 600 capsules. The blister strips are formed from PVC with a coating of PVdC backed with aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teofarma S.r.l.
Via Fratelli Cervi 8
Valle Salimbene
PV
27010
Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL 16250/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 July 1991

10 DATE OF REVISION OF THE TEXT

22/08/2023