SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MODUCREN, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Timolol maleate ..... 10 mg
Amiloride hydrochloride ..... 2.5 mg
Hydrochlorothiazide ..... 25 mg

Per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Arterial hypertension in cases where monotherapy with a beta-blocker or a diuretic has failed.

4.2 Posology and method of administration

Posology
The recommended dosage is **one tablet once daily**, preferably in the morning.
If blood pressure control is inadequate, re-evaluation of the treatment regimen is required.

Paediatric population
Since amiloride hydrochloride has not been studied in children, MODUCREN is **not recommended in paediatrics**.

Method of administration
Oral use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Related to timolol
This medicinal product must **never** be used in patients with:

- asthma or chronic obstructive pulmonary disease,
- heart failure not controlled by appropriate therapy,
- cardiogenic shock,
- second- or third-degree atrioventricular block not fitted with a pacemaker,

- Prinzmetal's angina,
- sinus node disease (including sino-atrial block),
- bradycardia (heart rate < 45–50 bpm),
- Raynaud's phenomenon or peripheral circulatory disorders,
- untreated pheochromocytoma,
- hypotension,
- hypersensitivity to timolol or excipients,
- concomitant use with floctafenine or sultopride (see section 4.5).

Related to hydrochlorothiazide and amiloride
Contraindicated in patients with:

- hypersensitivity to sulfonamides,
- moderate to severe renal impairment,
- hepatic encephalopathy,
- hyperkalaemia (serum potassium > 5.5 mmol/L),
- concomitant use with other potassium-sparing diuretics or potassium salts (except in hypokalaemia) (see section 4.5).

4.4 Special warnings and precautions for use

Special warnings

Related to timolol
Oral beta-blocker therapy must **never be discontinued abruptly**, especially in patients with angina: sudden withdrawal may lead to severe arrhythmias, myocardial infarction or sudden death.

Related to hydrochlorothiazide

Non-melanoma skin cancer (NMSC)
An increased risk of NMSC (basal cell carcinoma and squamous cell carcinoma) with cumulative exposure to hydrochlorothiazide has been observed in two epidemiological studies from the Danish cancer registry. Photosensitising effects of HCTZ may contribute to this risk.

Patients should be informed of this risk and advised to check their skin regularly and report any suspicious lesions. Preventive measures (limited sun/UV exposure, adequate protection) are recommended. Suspicious lesions should be examined promptly, including histologic assessment as appropriate. Use of HCTZ may require reconsideration in patients with a history of NMSC (see also section 4.8).

Choroidal effusion, acute myopia, and secondary angle-closure glaucoma
Sulfonamides or related derivatives may trigger an idiosyncratic reaction leading to choroidal effusion, visual field disturbances, transient myopia, and acute angle-closure glaucoma. Symptoms include sudden decreased visual acuity and ocular pain, usually occurring within hours to weeks of treatment

initiation. If intraocular pressure remains uncontrolled, medical or surgical intervention may be required. If untreated, angle-closure glaucoma may cause permanent vision loss.
The first step is to discontinue hydrochlorothiazide as soon as possible. A history of sulfonamide or penicillin allergy is a risk factor.

Acute respiratory toxicity
Very rare but severe cases of acute respiratory toxicity, including ARDS, have been reported after intake of hydrochlorothiazide. Pulmonary oedema usually develops within minutes to hours. Early symptoms include dyspnoea, fever, respiratory deterioration, and hypotension.
If ARDS is suspected, MODUCREN must be discontinued and appropriate treatment initiated. Hydrochlorothiazide must not be given again to patients who have previously experienced ARDS after exposure.

Related to hydrochlorothiazide and amiloride

Hyperkalaemia
Any medicinal product acting on the renin-angiotensin-aldosterone system (RAAS) can induce hyperkalaemia. This potentially life-threatening risk is increased in elderly patients, those with renal impairment or diabetes, or in combination with other hyperkalaemia-inducing drugs, or during intercurrent events (see section 4.5).

Before combining several RAAS inhibitors, the benefit–risk ratio must be carefully assessed.

Main risk factors for hyperkalaemia:

- diabetes, impaired renal function, age > 70 years;
- concomitant use of one or more RAAS blockers and/or potassium-increasing drugs (e.g.: potassium salts, potassium-sparing diuretics, ACE inhibitors, ARBs, NSAIDs including COX-2 inhibitors, heparins, immunosuppressants such as ciclosporin or tacrolimus, trimethoprim);
- intercurrent conditions: dehydration, acute heart failure, metabolic acidosis, renal impairment, sudden deterioration of general condition (e.g. infections), cellular lysis (e.g. limb ischaemia, rhabdomyolysis, extensive trauma).

Monitoring
A plasma electrolyte panel (potassium, sodium) and renal function must be assessed:

- before treatment initiation and again **one week to 15 days** later;
- before and after any dose increase or treatment modification;
- periodically during maintenance therapy, or in case of intercurrent events.

Hepatic impairment
Thiazide diuretics may precipitate hepatic encephalopathy; treatment must be discontinued immediately if this occurs.

Photosensitivity
Cases of photosensitivity have been reported. If this occurs, treatment should be stopped. If re-exposure is unavoidable, appropriate sun or UVA protection is required.

Precautions for use

Related to timolol

Discontinuation of therapy
Abrupt discontinuation must be avoided, especially in ischaemic heart disease. Dosage should be tapered gradually over 1 to 2 weeks. Substitute therapy may be introduced concurrently to prevent angina exacerbation.

Heart failure
In patients with controlled heart failure, treatment must be instituted under close medical supervision.

Bradycardia

If the resting heart rate falls below 50–55 beats per minute and the patient develops symptoms related to bradycardia, the dosage must be reduced.

First-degree atrioventricular block
Because of their negative dromotropic effect, beta-blockers should be administered with caution to patients with first-degree AV block.

Pheochromocytoma
Use of beta-blockers in hypertension due to treated pheochromocytoma requires close monitoring of blood pressure.

Elderly patients
Treatment should be initiated at a low dosage. Close monitoring is required throughout therapy.

Renal and hepatic impairment
(Except moderate to severe renal impairment, which is contraindicated—see section 4.3.) These conditions may require careful patient monitoring.

Diabetic patients
Patients must be warned and instructed to increase self-monitoring of blood glucose at treatment initiation.
Signs of hypoglycaemia—particularly tachycardia, palpitations and sweating—may be masked.

Psoriasis
Beta-blockers have been associated with worsening of psoriasis; the indication must be carefully considered.

Allergic reactions
In patients prone to severe anaphylactic reactions—regardless of the trigger—particularly to iodinated contrast media or floctafenine (see section 4.5), or during desensitisation procedures, beta-blocker therapy may worsen the reaction and reduce responsiveness to usual doses of adrenaline.

General anaesthesia
Beta-blockers attenuate reflex tachycardia and increase the risk of hypotension. Continuing beta-blocker therapy reduces the risk of arrhythmia, myocardial ischaemia and hypertensive surges. The anaesthetist must be informed that the patient is receiving a beta-blocker.

- If treatment withdrawal is considered necessary, interruption for 48 hours is generally sufficient to restore sensitivity to catecholamines.

- In some cases, beta-blocker treatment must not be discontinued:
    - in patients with coronary artery disease, treatment should ideally be continued until surgery due to the risks associated with abrupt withdrawal;
    - in emergencies or when interruption is not possible, the patient must be protected from excessive vagal tone through adequate atropine premedication, repeated if needed. Anaesthesia should use agents with minimal myocardial depressant effects, and blood loss should be compensated;
    - the increased risk of anaphylaxis associated with beta-blockers must be taken into account.

Thyrotoxicosis
Beta-blockers may mask certain signs, especially cardiovascular manifestations.

Related to hydrochlorothiazide and amiloride

Fluid and electrolyte balance

• Serum sodium
Must be checked before starting therapy and monitored regularly thereafter. Any diuretic may cause hyponatraemia, sometimes with severe consequences. Because early sodium decrease may be asymptomatic, regular monitoring is essential, especially in high-risk groups such as the elderly and cirrhotic patients (see sections 4.8 and 4.9).

• Serum calcium
Thiazide diuretics may reduce urinary calcium excretion and induce slight, transient hypercalcaemia. Overt hypercalcaemia may indicate previously unrecognised hyperparathyroidism. Discontinue treatment before evaluating parathyroid function.

• Blood glucose
Thiazide diuretics may cause modest hyperglycaemia. Diabetics must undergo systematic glucose monitoring.

• Uric acid
Sodium and water depletion induced by thiazides decreases uric acid excretion. In hyperuricaemic patients, gout attacks may be precipitated; dosage should be adjusted according to plasma uric acid levels.

• Renal function and diuretics
Thiazide diuretics are fully effective only when renal function is normal or slightly impaired (serum creatinine below ~25 mg/L, i.e., 220 µmol/L in adults, or creatinine clearance above 30 mL/min).

Renal function assessment

Serum creatinine may be misleading; renal function is better evaluated using electrolyte panels or formulas such as Cockcroft's equation:

Clcr = (140 − age) × weight / (0.814 × serum creatinine)

Where:

- age = years
- weight = kg
- serum creatinine = µmol/L

For women, multiply the result by 0.85.

Hypovolaemia secondary to diuretic-induced water and sodium loss may reduce glomerular filtration rate, leading to increased blood urea and creatinine.
This transient functional renal impairment is harmless in patients with normal renal function but may worsen pre-existing renal disease.

Reactions related to diuresis in cirrhotic patients

Adverse effects are more common in cirrhotic patients with ascites, who poorly tolerate electrolyte imbalance and often present baseline hypokalaemia due to secondary hyperaldosteronism.
Hepatic encephalopathy—manifested by tremor, confusion and coma—has occasionally been reported with amiloride hydrochloride alone or with hydrochlorothiazide.

In cirrhotics treated with amiloride hydrochloride alone, jaundice associated with underlying hepatic disease has worsened in a few cases, although causality is uncertain.

4.5 Interactions with other medicinal products and other forms of interaction

Related to timolol

Contraindicated combinations

+ Floctafenine
In cases of shock or hypotension induced by floctafenine, beta-blockers reduce cardiovascular compensatory mechanisms.

+ Sultopride
Increased risk of ventricular arrhythmias, particularly torsades de pointes.

Not recommended combinations

+ Amiodarone
Risk of impaired contractility, automaticity and conduction (suppression of compensatory sympathetic mechanisms).

Combinations requiring precautions for use

+ Halogenated volatile anaesthetics
Reduction of cardiovascular compensatory mechanisms by beta-blockers.
(Beta-adrenergic inhibition may be reversed during surgery using beta-stimulants.)
Beta-blocker therapy should generally not be discontinued abruptly. Inform the anaesthetist.

+ Calcium channel blockers (bepridil, diltiazem, verapamil)
Risk of severe bradycardia, sino-atrial block, AV block and heart failure (synergistic effects).
Combination only under strict clinical and ECG monitoring, particularly in elderly patients or at treatment initiation.

+ Antiarrhythmics (propafenone and class IA: quinidine, hydroquinidine, disopyramide)
Impaired contractility, automaticity and conduction.
Clinical and ECG monitoring required.

+ Clonidine, non-selective beta-blockers
Marked increase in blood pressure in case of abrupt withdrawal.
Avoid sudden discontinuation; ensure clinical monitoring.

+ Insulin and oral hypoglycaemic sulfonylureas
Beta-blockers may mask symptoms of hypoglycaemia (e.g., palpitations, tachycardia).
Warn patients and reinforce glucose self-monitoring, especially at treatment initiation.

+ Lidocaine *(reported with propranolol, metoprolol, nadolol)*
Increased plasma lidocaine levels due to reduced hepatic metabolism → potential neurological and cardiac toxicity.
Adjust lidocaine dosage; monitor clinically and via ECG; consider plasma levels.

+ Iodinated contrast media
In case of contrast-induced shock or hypotension, beta-blockers reduce cardiovascular compensation.
Stop beta-blockers before radiologic exposure whenever possible.
If discontinuation is impossible, ensure resuscitation equipment is available.

+ Tacrine
Risk of excessive bradycardia (additive bradycardic effects).
Requires regular clinical monitoring.

Combinations to be taken into account

+ NSAIDs
Reduced antihypertensive effect (NSAIDs inhibit vasodilatory prostaglandins; pyrazolone NSAIDs may cause sodium and water retention).

+ Calcium antagonists (dihydropyridines: amlodipine, felodipine, etc.)
Hypotension, heart failure in latent or uncontrolled cardiac insufficiency (negative inotropic effect).
Beta-blockers may suppress reflex sympathetic activation.

+ Mefloquine
Additive bradycardic effects → risk of bradycardia.

Related to hydrochlorothiazide and amiloride

Certain medicinal products or classes may increase the risk of hyperkalaemia:
potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin II antagonists, NSAIDs, heparins (LMWH or unfractionated), immunosuppressants (ciclosporin, tacrolimus), trimethoprim.

The combination of these substances increases the risk significantly, especially with potassium-sparing diuretics or potassium supplements.
ACE inhibitor + NSAID combinations carry a lower risk if precautions are followed.

Some medicines (e.g. trimethoprim) may contribute indirectly to hyperkalaemia when combined with other risk-increasing substances.

Not recommended combinations

+ Lithium

Increased serum lithium levels with signs of overdose, similar to what occurs with a low-sodium diet (reduced urinary lithium excretion).
If the combination cannot be avoided, strict monitoring of serum lithium levels and adjustment of lithium dosage are required.

+ Non-antiarrhythmic drugs associated with torsades de pointes
(e.g. astemizole, bepridil, IV erythromycin, halofantrine, pentamidine, sparfloxacin, terfenadine, vincamine)
(For sultopride, see "Contraindicated combinations related to timolol.")

Risk of torsades de pointes; hypokalaemia, bradycardia and pre-existing QT prolongation are predisposing factors.
Use substances that do not induce torsades de pointes in cases of hypokalaemia.

Combinations requiring precautions for use

+ Other hypokalaemic agents
Amphotericin B (IV), glucocorticoids and mineralocorticoids (systemic), tetracosactide, stimulant laxatives: increased risk of hypokalaemia (additive effect).
Monitor serum potassium and correct if necessary; particularly important when digitalis therapy is used. Prefer non-stimulant laxatives.

+ Digitalis glycosides
Hypokalaemia increases the risk of digitalis toxicity.
Monitor serum potassium and ECG if needed.

+ Potassium-sparing diuretics
(amiloride, potassium canrenoate, spironolactone, triamterene)
Although appropriate for some patients, the combination does not eliminate the risk of hypokalaemia or—especially in renal impairment or diabetes—hyperkalaemia.
Monitor serum potassium and ECG; reassess treatment if required.

+ Hypokalaemic diuretics
Similarly, this combination carries a risk of hypokalaemia or hyperkalaemia in susceptible patients.
Monitor serum potassium and ECG.

+ Antiarrhythmic drugs associated with torsades de pointes
(Class IA antiarrhythmics—quinidine, hydroquinidine, disopyramide—amiodarone, bretylium, sotalol)
Risk of torsades de pointes, favoured by hypokalaemia, bradycardia and prolonged QT interval.
Prevent and correct hypokalaemia; monitor QT interval.
In case of torsades, do **not** administer antiarrhythmics (use overdrive pacing).

+ Metformin
Risk of lactic acidosis triggered by functional renal impairment secondary to diuretics, especially loop diuretics.
Metformin must **not** be used if serum creatinine exceeds:

- 15 mg/L (135 µmol/L) in men
- 12 mg/L (110 µmol/L) in women

+ Iodinated contrast media
Diuretic-induced dehydration increases the risk of acute renal failure, particularly with high doses of contrast media.
Rehydrate before administration.

Combinations to be taken into account

+ Calcium salts
Risk of hypercalcaemia due to reduced urinary calcium excretion.

+ Ciclosporin, tacrolimus
Potentially life-threatening hyperkalaemia, especially in renal impairment (additive effects).

Related to the combination (amiloride + hydrochlorothiazide)

Contraindicated combinations

+ Other potassium-sparing diuretics
Amiloride, potassium canrenoate, triamterene
Risk of potentially life-threatening hyperkalaemia, especially in renal impairment.

+ Potassium salts
Risk of potentially life-threatening hyperkalaemia (additive effects), especially in renal impairment.

+ Sultopride
Increased risk of ventricular arrhythmias including torsades de pointes (favoured by hypokalaemia and bradycardia).

Not recommended combinations

(Unless hypokalaemia is present.)

+ ACE inhibitors (except in hypokalaemia)
Except spironolactone 12.5–50 mg/day in heart failure.
Risk of potentially life-threatening hyperkalaemia, especially in renal impairment.

+ Ciclosporin
Risk of functional renal impairment—even without sodium depletion—and potentially life-threatening hyperkalaemia (additive effects).

+ Angiotensin II receptor antagonists (ARBs)
Risk of potentially life-threatening hyperkalaemia, particularly in renal impairment.

Combinations requiring precautions for use

+ ACE inhibitors and ARBs

1. **Risk related to hydrochlorothiazide and amiloride**
   Risk of sudden hypotension and/or acute renal failure upon initiation of ACE inhibitors in patients with pre-existing sodium depletion (e.g. renal artery stenosis).

2. **Risk related to amiloride**
   With spironolactone 12.5–50 mg/day and ACE inhibitor doses < 75 mg captopril-equivalent or < 10 mg enalapril/lisinopril equivalent.

In NYHA class III–IV heart failure with ejection fraction < 35%, previously treated with ACE inhibitor + loop diuretic:
Risk of potentially life-threatening hyperkalaemia if prescription criteria are not strictly followed.

Before initiation, rule out hyperkalaemia and renal impairment.
Perform close biological monitoring of potassium and creatinine:

- weekly for the first month,
- then monthly.

+ Baclofen
Increased antihypertensive effect.
Monitor blood pressure and adjust diuretic dose if necessary.

+ NSAIDs
Risk of acute renal failure in susceptible patients (elderly, dehydrated) due to decreased glomerular filtration (inhibition of vasodilating prostaglandins).
Also decreased antihypertensive effect.
Ensure adequate hydration; monitor renal function at treatment initiation.

+ Acetylsalicylic acid (high anti-inflammatory doses ≥ 1 g per dose or ≥ 3 g/day)
Or analgesic/antipyretic doses (≥ 500 mg per dose and < 3 g/day):
Risk of acute renal failure in dehydrated patients (reduced renal prostaglandin synthesis).
Reduced antihypertensive effect.
Hydrate and monitor renal function.

Combinations to be taken into account

+ Imipramine-like antidepressants, neuroleptics
Increased antihypertensive effect and risk of orthostatic hypotension (additive effect).

+ Corticosteroids
Reduced antihypertensive effectiveness (sodium/water retention).

+ Alpha-blockers used in urology
(alfuzosin, doxazosin, prazosin, tamsulosin, terazosin)
Increased hypotensive effect; higher risk of orthostatic hypotension.

+ Antihypertensive alpha-blockers
Increased hypotensive effect; risk of orthostatic hypotension.

+ Amifostine
Increased hypotension (additive effect).

+ Other hyperkalaemia-inducing drugs
Increased risk of potentially life-threatening hyperkalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Related to timolol
Animal studies have not shown teratogenic effects.
In clinical use, no teratogenic effects have been reported to date; controlled prospective studies with beta-blockers have not demonstrated congenital malformations.

In mothers treated with beta-blockers, neonatal beta-blockade may persist for several days after birth. Although usually asymptomatic, cases of neonatal heart failure requiring intensive care (see section 4.9), bradycardia, respiratory distress and hypoglycaemia have been reported.
Volume expansion must be avoided (risk of pulmonary oedema).

Related to amiloride
No reliable teratogenicity data are available in animals.
In humans, no sufficient clinical data exist to assess a potential risk of malformation or fetotoxicity when used during pregnancy.

Related to hydrochlorothiazide
Thiazide diuretics should generally be avoided during pregnancy and must not be used to treat physiological oedema of pregnancy. They may cause fetoplacental ischaemia with a risk of fetal growth retardation.
Rare cases of fetal or neonatal jaundice and severe neonatal thrombocytopenia have been reported.

MODUCREN is not recommended during pregnancy.

Breastfeeding

Breastfeeding is **not recommended** during treatment with MODUCREN.

4.7 Effects on ability to drive and use machines

Use of this medicinal product may cause **drowsiness**, posing risks for patients driving vehicles or operating machinery.

4.8 Undesirable effects

Related to timolol

The most frequent adverse reactions are generally mild:

- gastrointestinal disorders (dyspepsia, nausea, vomiting, diarrhoea),
- asthenia,
- insomnia, nightmares, depression,
- Raynaud's syndrome, cold extremities or paraesthesia.

Rarely: impotence.

Possible occurrences:

- severe bradycardia; if present, atrioventricular block, hypotension, worsening of angina,

- heart failure,
- asthma attacks,
- hypoglycaemia (see section 4.4),
- worsening of pre-existing intermittent claudication.

Infrequently reported:

- cutaneous manifestations including urticaria, angioedema (Quincke's oedema), psoriasiform rash (see section 4.4).

Related to the combination hydrochlorothiazide + amiloride

- headache, muscle weakness, asthenia, malaise, chest or back pain,
- arrhythmia, tachycardia, orthostatic hypotension, angina, signs of digitalis toxicity,
- anorexia, nausea, vomiting, diarrhoea, constipation, abdominal pain, gastrointestinal bleeding, appetite disorders, abdominal bloating, thirst, hiccups,
- increased serum potassium (> 5.5 mEq/L), gout, dehydration with hypovolaemia, hyponatraemia requiring dose reduction or discontinuation,
- rash, pruritus, flushing,
- leg pain, muscle cramps, arthralgia,
- dizziness, vertigo, paraesthesia, lethargy,
- insomnia, nervousness, confusion, depression, drowsiness,
- dyspnoea,
- transient visual disturbances, nasal congestion, dysgeusia,
- impotence, dysuria, nocturia, incontinence.

Additional adverse effects reported with individual components

Amiloride hydrochloride

- hepatic function abnormalities,
- activation of a pre-existing peptic ulcer,
- anorexia, nausea, vomiting, abdominal pain or bloating, constipation, diarrhoea,
- dry mouth, thirst, paraesthesia, dizziness, general weakness, fatigue, muscle cramps, orthostatic hypotension,
- risk of hyperkalaemia, encephalopathy (see section 4.4), hyponatraemia, aplastic anaemia, neutropenia,
- rash, pruritus,
- headache, chest pain,

- psychiatric symptoms: confusion, drowsiness, transient visual disturbances,
- cough, dyspnoea.

Hydrochlorothiazide

- nausea, constipation, dizziness, asthenia, paraesthesia, headache (rare and usually dose-related),
- possible exacerbation of pre-existing systemic lupus erythematosus; very rare Lyell's syndrome,
- anaphylactic shock, fever,
- necrotising vasculitis,
- cholestatic hepatitis, pancreatitis;
  in hepatic impairment, risk of hepatic encephalopathy (see sections 4.3 and 4.4),
- glycosuria, hyperglycaemia, hyperuricaemia, rare hypercalcaemia,
- infrequent: photosensitivity reactions (see section 4.4), hypersialorrhoea, urticaria,
- restless legs syndrome,
- respiratory distress, pneumonia,
- transient blurred vision, xanthopsia,
- agranulocytosis, bone marrow aplasia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia,
- potassium depletion with hypokalaemia—particularly severe in high-risk groups,
- hyponatraemia with hypovolaemia leading to dehydration, orthostatic hypotension, confusion; associated chloride loss may cause compensatory metabolic alkalosis (usually mild),
- increase in plasma lipids at high doses,
- benign, malignant and unspecified tumours (including cysts and polyps),
- **frequency "unknown": non-melanoma skin cancer** (basal cell carcinoma, squamous cell carcinoma), ocular disorders (choroidal effusion, acute myopia, angle-closure glaucoma),
- **very rare**: acute respiratory distress syndrome (ARDS) (see section 4.4).

Description of selected adverse reactions

Non-melanoma skin cancer (NMSC):
Epidemiological data show a cumulative, dose-dependent association between hydrochlorothiazide and NMSC (see sections 4.4 and 5.1).
One study of 71,533 BCC cases and 8,629 SCC cases, matched to population controls, found:

- adjusted OR 1.29 (95% CI: 1.23–1.35) for BCC;
- adjusted OR 3.98 (95% CI: 3.68–4.31) for SCC for high cumulative use (≥50,000 mg).

Another study on 633 lip cancer (SCC) cases showed a cumulative dose-response:

- adjusted OR 2.1 (95% CI: 1.7–2.6) increasing to
- OR 3.9 (~25,000 mg cumulative) and
- OR 7.7 (~100,000 mg cumulative).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing authorisation is important to allow continuous monitoring of the benefit-risk balance of the medicinal product.
Healthcare professionals should report any suspected adverse reaction via the national reporting system:
Agence nationale de sécurité du médicament et des produits de santé (ANSM) and the **Regional Pharmacovigilance Centres** network — website:
https://signalement.social-sante.gouv.fr/

4.9 Overdose

Related to amiloride hydrochloride

No human data are available. It is unknown whether the drug is dialysable.
Most likely signs include dehydration and electrolyte imbalance.
MODUCREN must be discontinued and the patient carefully monitored.
There is no specific antidote; treatment is symptomatic.
Effective measures must be taken in cases of hyperkalaemia.

Related to hydrochlorothiazide

Acute intoxication primarily manifests as fluid and electrolyte disturbances (hyponatraemia, hypokalaemia).
Clinical manifestations may include nausea, vomiting, hypotension, muscle cramps, dizziness, somnolence, confusion, polyuria or oliguria, potentially progressing to anuria (due to hypovolaemia).
Initial management consists of restoring fluid and electrolyte balance in a specialised setting.
Hyponatraemia must be corrected **very gradually**.

Related to timolol

In cases of severe bradycardia or excessive hypotension, administer IV:

- atropine 1–2 mg bolus,
- glucagon 10 mg slow bolus, followed if needed by infusion 1–10 mg/hour,
- if necessary, either isoprenaline 15–85 µg slow IV injection (repeatable; total dose ≤ 300 µg), or dobutamine 2.5–10 µg/kg/min.

In neonatal cardiac decompensation after maternal beta-blocker exposure:

- glucagon 0.3 mg/kg,
- intensive care admission,
- isoprenaline and dobutamine (high doses and prolonged treatment require expert monitoring).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **Beta-blocking agents, thiazides and related diuretics**, ATC code: **C07DA06**.

Antihypertensive medicinal product combining the properties of:

- **hydrochlorothiazide:** a diuretic increasing sodium and chloride excretion,
- **amiloride hydrochloride:** a potassium- and magnesium-sparing diuretic,
- **timolol maleate:** a beta-blocker without local anaesthetic effect and without intrinsic sympathomimetic activity.

Their antihypertensive actions are additive.
At the studied doses, MODUCREN showed superior antihypertensive effect compared with timolol alone and with the amiloride + hydrochlorothiazide combination.

Magnesium excretion with the amiloride–hydrochlorothiazide combination is lower than with thiazide or loop diuretics alone.

Hydrochlorothiazide effects:

- onset approx. 2 hours after dosing,
- peak diuretic and natriuretic effect around 4 hours,
- diuretic activity sustained for approx. 12 hours.

Amiloride:

- onset ~2 hours after administration,
- peak potassium-sparing effect between 6 and 10 hours.

Non-melanoma skin cancer:
Based on available epidemiological data, a cumulative, dose-dependent association between hydrochlorothiazide (HCTZ) and non-melanoma skin cancer (NMSC) has been observed.

One study included **71,533 cases of basal cell carcinoma (BCC)** and **8,629 cases of squamous cell carcinoma (SCC)**, matched with **1,430,833** and **172,462** population controls, respectively.
High cumulative HCTZ exposure (≥ 50,000 mg) was associated with:

- an adjusted **odds ratio (OR)** of **1.29** (95% CI: 1.23–1.35) for BCC,
- and **3.98** (95% CI: 3.68–4.31) for SCC.

A clear cumulative dose–response relationship was observed for both BCC and SCC.

Another study showed a possible association between HCTZ and **lip cancer (SCC)**:

- 633 cases of lip cancer were matched to 63,067 population controls using risk-set sampling. A cumulative dose–response relationship was demonstrated with an adjusted OR of **2.1** (95% CI: 1.7–2.6), increasing to:

- OR **3.9** (3.0–4.9) for ~25,000 mg cumulative use,
- and OR **7.7** (5.7–10.5) for the highest cumulative dose (~100,000 mg).

(See also section 4.4.)

5.2 Pharmacokinetic properties

Hydrochlorothiazide

Hydrochlorothiazide is rapidly absorbed (60–80%).
The elimination half-life is approximately:

- **1.7 hours** during the first 10 hours, then
- **5.6 to 14.8 hours** thereafter.

Elimination occurs mainly via the kidneys (70% within 48 hours) as unchanged drug through glomerular filtration and tubular secretion.
Hydrochlorothiazide crosses the placental barrier and is excreted in breast milk.

Timolol

Timolol maleate is rapidly absorbed after oral administration: plasma levels become measurable within **30 minutes** and persist for about **12 hours**.
Peak plasma concentration is reached within **1–2 hours**.
Elimination of timolol and its metabolites is predominantly renal.
The elimination half-life is **4–5 hours**.
Timolol is excreted renally after partial hepatic metabolism.

In women, the plasma-to-milk concentration ratio averages around **0.8**.

Amiloride

Amiloride is partially absorbed through the gastrointestinal tract.
Peak serum concentration occurs **3–4 hours** after administration.
It is excreted unchanged in the urine.
The elimination half-life is approximately **6 hours**.

The bioavailability of each MODUCREN component is equivalent to that observed when the substances are administered separately.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Microcrystalline cellulose
- Starch STA-RX 1500
- Indigo carmine (E132)

- Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special storage conditions.

6.5 Nature and contents of container

30 tablets in PVC/Aluminium blister packs.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATOIRES FRILAB
104 Boulevard Auguste Blanqui
75013 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

• **34009 322 093 7 8**: 30 tablets in PVC/Aluminium blisters.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

[To be completed later by the Marketing Authorisation Holder]

10. DATE OF REVISION OF THE TEXT

[To be completed later by the Marketing Authorisation Holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

PRESCRIPTION AND DISPENSING CONDITIONS

List I – Prescription-only medicine.