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FACULTAT DE FARMÀCIA I CIÈNCIES DE L'ALIMENTACIÓ

Final Degree Project

Pharmacy Degree

TELMISARTAN 40 MG TABLETS

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Pharmaceutical Technology,
Biopharmacy and Pharmacokinetics, Physiology and Pathophysiology,
Legislation

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ABBREVIATIONS

ABPM - Ambulatory Blood Pressure Monitoring

ACE - Angiotensin-Converting Enzyme

ACE-i - Angiotensin-Converting Enzyme Inhibitors

ADME - Absorption, Distribution, Metabolism, and Excretion

AEMPS - Agencia Española de Medicamentos y Productos Sanitarios

ANP - Atrial Natriuretic Peptide

ARB - Angiotensin II Receptor Blocker

AT1 - Angiotensin II Type 1 Receptor

AT2 - Angiotensin II Type 2 Receptor

AUC - Area Under the Curve

BCS - Biopharmaceutics Classification System

BP - Blood Pressure

CN - National Code

CV - Cardiovascular

DBP - Diastolic Blood Pressure

eGFR - Estimated Glomerular Filtration Rate

EMA - European Medicines Agency

GIT - Gastrointestinal Tract

GMP - Good Manufacturing Practice

HF - Heart Failure

HSA - Human Serum Albumin

LV - Left Ventricle

LVEF - Left Ventricular Ejection Fraction

LVH - Left Ventricular Hypertrophy

MCC - Microcrystalline Cellulose

MI - Myocardial Infarction

MRA - Mineralocorticoid Receptor Antagonists

NSAIDs - Non-Steroidal Anti-Inflammatory Drugs

PBPK - Physiologically Based Pharmacokinetic Modeling

PEG - Polyethylene Glycol

Ph. Eur. - European Pharmacopoeia

PIL - Patient Information Leaflet

PPAR-γ - Peroxisome Proliferator-Activated Receptor Gamma

RAAS - Renin-Angiotensin-Aldosterone System

SBP - Systolic Blood Pressure

SIGRE - Sistema Integrado de Gestión y Reciclaje de Envases

TAMC - Total Aerobic Microbial Count

TYMC - Total Yeasts and Molds Count

ZFP - Zero Filling Pressure

ABSTRACT

This final degree project explores Telmisartan 40 mg tablets, focusing on their pharmacological profile, formulation strategies, and industrial manufacturing process.

Telmisartan, a BCS Class II drug, has low solubility and high permeability, making its bioavailability a challenge. This work reviews various solubility enhancement techniques, ultimately selecting solid dispersion with PEG 6000 as the most effective approach to improve dissolution and absorption.

A comprehensive manufacturing proposal is presented, detailing the preparation of solid dispersions using the fusion method, followed by sieving, blending, and tablet compression. In-process and finished product quality control tests are outlined to ensure compliance with European Pharmacopoeia standards. Additionally, primary and secondary packaging designs are proposed to optimize stability, patient safety, and regulatory requirements

The work also emphasizes environmental sustainability, incorporating eco-friendly materials and Spain's SIGRE recycling system to reduce pharmaceutical waste. By integrating advanced formulation techniques and sustainable practices, this bibliographic study contributes to the development of an effective, high-quality, and environmentally responsible Telmisartan formulation.

Keywords: Telmisartan, solubility enhancement, solid dispersion, tablet formulation, pharmaceutical manufacturing, pharmacokinetics, sustainability.

RESUMEN

Este trabajo de fin de grado explora las tabletas de Telmisartán de 40 mg, centrándose en su perfil farmacológico, estrategias de formulación y proceso de fabricación industrial.

Telmisartán, un fármaco de Clase II según el BCS, tiene baja solubilidad y alta permeabilidad, lo que representa un desafío para su biodisponibilidad. Este trabajo revisa diversas técnicas de mejora de la solubilidad, seleccionando finalmente la dispersión sólida con PEG 6000 como el enfoque más eficaz para mejorar la disolución y absorción.

Se presenta una propuesta integral de fabricación, detallando la preparación de dispersiones sólidas mediante el método de fusión, seguido de tamizado, mezcla y compresión de tabletas. Se describen las pruebas de control de calidad en proceso y del producto terminado para garantizar el cumplimiento de los estándares de la Farmacopea Europea.

Además, se proponen diseños de envasado primario y secundario para optimizar la estabilidad, la seguridad del paciente y los requisitos regulatorios.
El trabajo también enfatiza la sostenibilidad ambiental, incorporando materiales ecológicos y el sistema de reciclaje SIGRE de España para reducir los residuos farmacéuticos. Al integrar técnicas avanzadas de formulación y prácticas sostenibles, este estudio bibliográfico contribuye al desarrollo de una formulación de Telmisartán eficaz, de alta calidad y ambientalmente responsable.

Palabras clave: Telmisartán, mejora de la solubilidad, dispersión sólida, formulación de tabletas, fabricación farmacéutica, farmacocinética, sostenibilidad.

Integration of Teaching Areas

The main teaching area of my final degree project in Pharmacy corresponds to the Pharmaceutical Technology, as this project focuses on a proposal for reformulation of Telmisartan, aiming to improve its solubility and bioavailability. The study involves exploring various excipients and optimizing the pharmaceutical form to enhance its effectiveness. Additionally, it focuses on ensuring an efficient industrial manufacturing process for the production of Telmisartan with a dose that meets therapeutic requirements. On the other hand, efficient production methods, along with the use of sustainable materials for packaging, are explored to minimize environmental impact while maintaining the quality of the pharmaceutical product.

Next, the Biopharmacy and Pharmacokinetics field is also an integral area to this project. A key aspect of the work involves understanding the pharmacodynamics and pharmacokinetics of Telmisartan, which is essential for selecting the most appropriate formulation methods. This knowledge is crucial to ensure that the drug's absorption, distribution, metabolism, and elimination align with its therapeutic goals, while also minimizing potential adverse effects.

The field of Physiology and Pathophysiology is relevant, particularly in relation to hypertension, the condition for which Telmisartan is commonly prescribed. Understanding the underlying mechanisms of hypertension, its impact on the cardiovascular system, and the diagnostic methods used to assess and treat the disease, allows for a more comprehensive evaluation of Telmisartan's therapeutic role in improving patients' quality of life.

Finally, the Legislation area is a critical component, as the regulatory framework for the development and marketing of pharmaceutical products is essential. Telmisartan, like all pharmaceutical products, must comply with current laws and regulations. This includes aspects related to safety, efficacy, and the information that must be provided in the packaging. Furthermore, sustainability considerations are factored into the packaging design, ensuring that Telmisartan's packaging aligns with responsible production practices.

Sustainable Development Goals (SDGs):

This research on Telmisartan directly contributes to the achievement of several United Nations Sustainable Development Goals (SDGs), focusing on improving global health, fostering innovation in the pharmaceutical industry, and promoting responsible consumption and production. Specifically, this thesis addresses the following SDGs:

- SDG 3: Good Health and Well-being

The primary objective of this research is to explore Telmisartan as a therapeutic option for the treatment of hypertension, contributing to the global effort to ensure healthy lives and promote well-being for all at all ages. Hypertension is a leading cause of cardiovascular diseases, which account for a significant portion of global morbidity and mortality. By improving the therapeutic use of Telmisartan, this research directly supports SDG 3 by addressing the health needs of individuals suffering from hypertension, particularly in low- and middle-income countries where access to effective treatments is crucial. Furthermore, this study helps to advance the development of safer, more effective pharmaceutical solutions for the management of chronic diseases.

- SDG 9: Industry, Innovation, and Infrastructure

SDG 9 focuses on building resilient infrastructure, promoting sustainable industrialization, and fostering innovation. The pharmaceutical industry plays a key role in this context, with the development and production of Telmisartan contributing to economic growth, job creation, and technological advancements. Through the formulation and optimization of Telmisartan, this research supports the ongoing innovation in the pharmaceutical sector, particularly in improving drug delivery systems and addressing solubility challenges. By introducing new formulations and optimizing production methods, this research contributes to sustainable industrial practices that minimize environmental impact and enhance the efficiency of pharmaceutical manufacturing processes. These advancements help strengthen the infrastructure of the pharmaceutical industry while encouraging continuous innovation to meet public health needs.

- SDG 12: Responsible Consumption and Production

SDG 12 emphasizes sustainable consumption and production, especially in resource-intensive industries like pharmaceuticals. Telmisartan, as a once-a-day medication, helps reduce waste by improving adherence and minimizing overuse. This research also explores efficient manufacturing processes and sustainable packaging materials, aligning with SDG 12 to promote responsible practices in the pharmaceutical sector.

By integrating these SDGs into the research on Telmisartan, this thesis not only addresses critical public health issues but also supports global efforts towards sustainability, innovation, and responsible industry practices. These connections to SDG 3, SDG 9, and SDG 12 demonstrate the broader societal impact of this research, reinforcing its importance in advancing both scientific knowledge and sustainable development.

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1. INTRODUCTION

Hypertension, commonly known as high blood pressure, is a major global health concern and one of the leading risk factors for cardiovascular diseases and chronic kidney disease. It affects more than one billion people worldwide, and its prevalence is increasing due to factors such as aging populations, sedentary lifestyles, unhealthy diets, and obesity. Hypertension is a chronic condition in which the force of blood against the walls of the arteries remains consistently high, placing excessive strain on the cardiovascular system. Blood pressure is determined by the amount of blood the heart pumps and the resistance of the arteries to blood flow. When this balance is disrupted - due to factors such as increased vascular resistance, excessive sodium retention, or overactivation of the renin-angiotensin-aldosterone system - blood pressure rises and, if left untreated, can lead to severe complications, including damage to vital organs such as the heart, kidneys, and brain. Chronic hypertension contributes to the thickening and stiffening of arterial walls, reducing their elasticity and increasing the risk of atherosclerosis, a condition that can further lead to ischemic events such as heart attacks and strokes. In addition, high blood pressure can overwork the heart, leading to left ventricular hypertrophy and, eventually, heart failure. In the kidneys, sustained hypertension can impair filtration, leading to chronic kidney disease and, in severe cases, kidney failure. Furthermore, hypertension is closely linked to cognitive decline and vascular dementia due to its effects on cerebral blood flow. Managing blood pressure effectively is essential to reducing the risk of these life-threatening conditions. (1, 2)

Many types of medications available to lower blood pressure, but not all patients respond equally to treatment. Among the different drug classes, angiotensin II receptor blockers (ARBs) have gained attention due to their ability to control blood pressure effectively while also offering additional protective effects for the heart and kidneys. Telmisartan, a widely used ARB, works by blocking the angiotensin II type 1 (AT_1) receptor, which prevents blood vessels from narrowing and helps lower blood pressure. In addition to its role in hypertension management, Telmisartan has unique properties, such as a long duration of action and the ability to partially activate peroxisome proliferator-activated receptor gamma (PPAR-γ), which may offer added benefits for patients with metabolic disorders such as diabetes. (3, 4)

Despite its advantages, Telmisartan has challenges related to its formulation because it has very low solubility in water. This makes it difficult for the body to absorb the drug efficiently, potentially reducing its effectiveness. To overcome this issue, researchers have developed different formulation strategies, including solid dispersions and cyclodextrin complexes, to improve its dissolution and absorption. (5)

This research project will provide a detailed analysis of Telmisartan, covering its effects on the body, its medical uses, and the challenges in its formulation. Additionally, it will explore different strategies to improve its solubility and absorption, ensuring better treatment outcomes for patients. By reviewing scientific studies and clinical data, this work aims to provide a well-structured evaluation of Telmisartan's role in treating hypertension and the potential improvements that can be made in its formulation.

1.1. Hypertension

Blood pressure is the force exerted by the blood against the walls of the arteries as the heart pumps it around the body. It is measured in millimeters of mercury (mmHg) and is recorded as two numbers:

- Systolic Pressure: The first (higher) number represents the pressure in your arteries when your heart beats.
- Diastolic Pressure: The second (lower) number represents the pressure in your arteries when your heart rests between beats.

A normal blood pressure reading is typically around 120/80 mmHg. Hypertension is diagnosed when blood pressure consistently exceeds 130/80 mmHg.

Primary hypertension, also known as essential hypertension, is the most common type of high blood pressure. It develops gradually over time with no identifiable single cause. Instead, it is believed to result from a combination of genetic, environmental, and lifestyle factors.

Secondary hypertension is caused by an underlying medical condition or the use of certain medications. Unlike primary hypertension, secondary hypertension tends to develop suddenly and may be more severe. It can result from kidney diseases, such as chronic kidney disease or polycystic kidney disease, which disrupt the body's ability to regulate blood pressure. Hormonal disorders can also contribute to hypertension. Certain medications like birth control pills, decongestants, and non-steroidal anti-inflammatory drugs (NSAIDs) may increase blood pressure as a side effect. (1, 2)

1.2. Introduction to the renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) is a critical regulator of blood volume, electrolyte balance, and systemic vascular resistance. While the baroreceptor reflex responds in the short-term to decreased arterial pressure, the RAAS is responsible for acute and chronic alterations. The classical understanding of RAAS is that it comprises 3 significant compounds: renin, angiotensin II, and aldosterone. These 3 compounds elevate arterial pressure in response to decreased renal blood pressure, salt delivery to the distal convoluted tubule, and beta-agonism. The understanding of RAAS has expanded tremendously due to discoveries of newer system components over the last few decades. The discussion on this topic is limited to the components of the classical pathway of the RAAS. (6)

The RAAS is ubiquitous and involves multiple organ systems, especially the kidneys, lungs, systemic vasculature, adrenal cortex, and brain. The RAAS is a crucial mediator of cardiac, vascular, and renal physiology through regulating vascular tone and salt and water homeostasis. In addition to the main physiological functions, the RAAS has a significant role in the pathophysiological conditions of hypertension, heart failure, other cardiovascular diseases, and renal diseases. (6)

Renin:

Renin is an enzyme secreted by juxtaglomerular cells in the kidney. It is formed from prorenin and stored in granules. Its release is triggered by:

- Low renal perfusion (sensed by mechanoreceptors in afferent arterioles).
- Reduced sodium/chloride levels at the macula densa.
- Increased sympathetic activation via β1-adrenergic receptors.
- Feedback from angiotensin I, potassium, and atrial natriuretic peptide (ANP).

Renin converts angiotensinogen, a protein secreted by the liver, into angiotensin I, which has no biological activity. Angiotensin-Converting Enzyme (ACE) then transforms angiotensin I into angiotensin II, the key molecule in RAAS. ACE is expressed on plasma membranes of vascular endothelial cells, primarily in the pulmonary circulation. It cleaves the 2 amino acids from the C-terminal of angiotensin I to make the peptide angiotensin II. (7)

Angiotensin II and Its Effects:

Angiotensin II has a short half-life in circulation (less than 60 seconds) and plays a crucial role in blood pressure and fluid balance by:

- **Vasoconstriction**: Contracts vascular smooth muscle, increasing blood pressure.
- **Aldosterone secretion:** Stimulates the adrenal cortex, leading to sodium and water retention.

- **Sodium reabsorption:** Increases Na_1 reuptake in the proximal tubule.
- **Sympathetic activation:** Enhances nervous system stimulation.
- **Vasopressin release:** Stimulates the hypothalamus to retain water.

Angiotensin II is also implicated in many pathophysiological states and is known to induce oxidative stress, vascular smooth muscle contraction, endothelial dysfunction, fibrosis, and hypertrophic, anti-apoptotic, and pro-mitogenic effects (Figure 1). (7)

Angiotensin II has been implicated in the pathogenesis of hypertension, atherosclerotic disease, heart failure, and kidney disease through these effects. The physiological and pathophysiological effects of angiotensin II are mediated by 2 types of receptors: type 1 and type 2. These receptors have different and often opposing physiological responses. (7)

Angiotensin Receptors: AT1 vs. AT2

AT1 Receptor (AT1R):

- Found in the heart, kidneys, and blood vessels.
- Mediates vasoconstriction, sodium retention, and fibrosis.
- Excessive activation is linked to cardiovascular and renal diseases.

AT2 Receptor (AT2R):

- Mainly present in fetal tissues; in adults, it is found in the heart, kidneys, and brain.
- Opposes AT1R effects, promoting vasodilation and reducing inflammation. (7)

Aldosterone:

Aldosterone, synthesized in the adrenal cortex, regulates sodium and potassium balance. It acts through mineralocorticoid receptors, increasing sodium reabsorption and potassium excretion in the kidneys. It also affects thirst and salt appetite, influencing overall fluid homeostasis. Overactivation of the RAAS has been implicated in the pathogenesis of various cardiovascular and renal diseases, including primary hypertension and secondary hypertension due to primary hyperaldosteronism. Primary hyperaldosteronism is the excess aldosterone production either by an adrenal adenoma (Conn syndrome) or bilateral adrenal hyperplasia producing excess aldosterone. This condition remains under-recognized with excess cardiovascular and renal morbidity and mortality. (7)

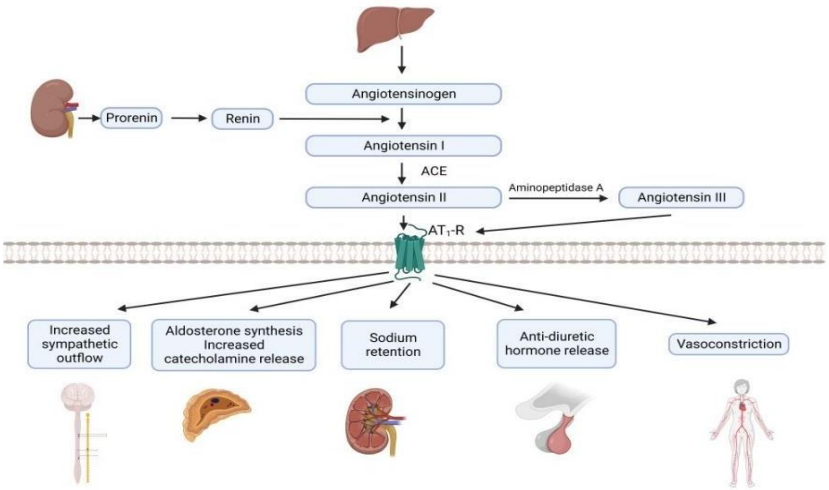

Figure 1: The renin-angiotensin-aldosterone system. (7)

1.3. Medications targeting the renin-angiotensin-aldosterone system

- Direct Renin Inhibitor: Aliskiren has not improved renal or cardiovascular outcomes. The use of these agents remains uncommon in clinical practice.
- Angiotensin-Converting Enzyme inhibitors (ACE-i): Commonly used agents include lisinopril, captopril, ramipril, enalapril, fosinopril, and benazepril. These agents have improved cardiovascular outcomes and certain kidney outcomes, even in patients with type 2 diabetes.
- Angiotensin Receptor Blockers (ARB): Commonly used agents include valsartan, candesartan, irbesartan, olmesartan, and telmisartan. These are used as first-line agents for the management of hypertension. Multiple agents have been shown to improve cardiovascular outcomes, including reduced heart failure and cardiovascular mortality hospitalizations. These agents have been shown to improve certain kidney outcomes, such as reducing microalbuminuria and slowing the progression of kidney disease, even in patients with type 2 diabetes. Telmisartan works by blocking the vasoconstrictor and aldosterone secretory effects of angiotensin II.
- Mineralocorticoid Receptor Antagonists (MRA): Spironolactone, eplerenone, and finerenone have improved outcomes in patients with a history of heart failure. These medications are the first-line agents for cases of primary hyperaldosteronism. (Figure 2)
- Aldosterone Synthase Blocker: Baxdrostat, a selective aldosterone synthase inhibitor, has shown results in patients with resistant hypertension.

These agents result in a reduction in vasoconstriction and improved renal perfusion. Blockade of components of RAAS also leads to decreased inflammation, hypertrophy, and fibrosis. This results in a reduction in tissue remodeling in the cardiac and renal tissues. (8)

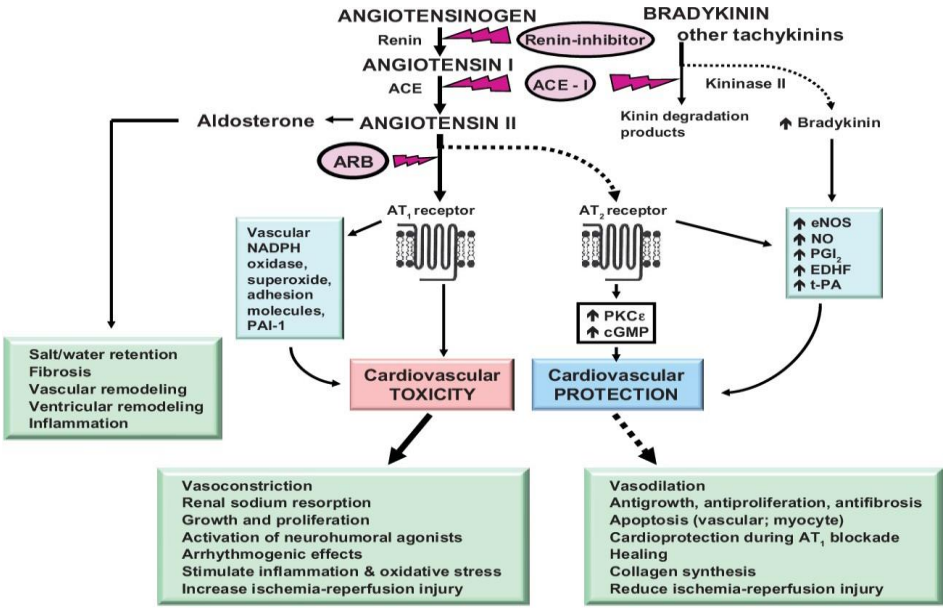

Figure 2: Mechanism of action. (8)

1.4. Drug development and history of telmisartan

Telmisartan is an angiotensin II receptor blocker (ARB) primarily used to treat hypertension and reduce cardiovascular risk. It was discovered and developed by Boehringer Ingelheim as part of efforts to create a long-acting ARB with enhanced tissue penetration and unique metabolic effects. Telmisartan's distinct pharmacological profile contributed to its widespread adoption, as it was found to have partial PPAR-γ activity, giving it potential metabolic benefits beyond blood

pressure control. Over time, large-scale clinical trials, such as ONTARGET and TRANSCEND, demonstrated its cardiovascular protective effects, further increasing its popularity. (3)

As telmisartan's effectiveness became evident, its use expanded rapidly and the drug gained significant market share worldwide, competing with other ARBs like losartan, valsartan, and irbesartan due to its longer duration of action (24 hours) and higher lipophilicity, allowing for better tissue penetration. (3)

Telmisartan's patent protection, originally expired in 2014, allowing multiple pharmaceutical companies to manufacture generic versions. Over time, its affordability improved, and it became one of the most prescribed ARBs worldwide, available under different trade names such as Pritor, Telma, and Micardis. Its growing reputation as a versatile ARB with additional cardiometabolic benefits continues to drive its global demand, making it an essential drug in hypertension treatment guidelines. (9)

1.5. General overview of telmisartan

Telmisartan is an angiotensin II receptor antagonist used to treat high blood pressure, and kidney problems in diabetes, and slow the progress of heart failure. In this part, its chemical structure, molecular properties, solubility, pKa values, and stability conditions are discussed. (10)

Chemical structure:

The chemical structure of Telmisartan is shown in Figure 3. (10)

IUPAC name:

4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid.

Chemical name of this compound, computed from its structure based on the International Union of Pure and Applied Chemistry (IUPAC) nomenclature standards. (10)

Molecular formula: $C_{11}H_{11}N_1O_1$

Molecular weight: 514.63 g/mol

SMILES:
CCCC1=NC2=C(C=C(C=C2C)C2=NC3=CC=CC=C3N2C)N1CC1=CC=C(C=C1)C1=CC=CC=C1C(O)=O
The Simplified Molecular Input Line Entry System (SMILES) is a widely-used line notation for chemical structures. (10)

European Community (EC) number: 620-494-7

The European Community (EC) number is a seven-digit identifier assigned by the European Chemicals Agency (ECHA) to substances for regulatory purposes within the European Union. (10, 11)

CAS: 144701-48-4

A CAS Registry Number is a proprietary registry number assigned by the Chemical Abstracts Service (CAS) division of the American Chemical Society (ACS). (10, 11)

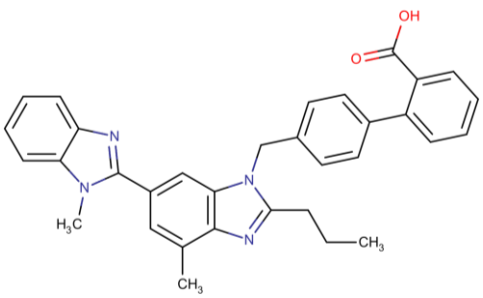

Figure 3: The chemical structure of Telmisartan (10)

1.6. Physical state and appearance

Physical description: Solid

Color / Form: White to slightly yellowish solid. It is odorless and it exists as a solid at room temperature.
Melting Point: 261-263 °C

Solubility: Practically insoluble in water and in the pH range of 3 to 9 which affects its absorption and formulation strategies.Sparingly soluble in strong acid (except insoluble in hydrochloric acid) and soluble in strong base. Solubility in Organic Solvents: Telmisartan is sparingly soluble in ethanol and methanol. (10)

LogP: 7.7

Log P is the partition coefficient expressed in logarithmic form, representing the ratio of a compound's concentrations in two immiscible solvents at equilibrium. A Log P value of 7.7 indicates that Telmisartan is highly lipophilic, meaning it has a greater affinity for lipids than for water. This high lipophilicity contributes to its very low aqueous solubility, which presents challenges for formulation and bioavailability. (10)

pKa Values: Telmisartan has two benzimidazole groups and a carboxylic acid group, with pKa values of 4.57, 5.86, and 3.62, respectively. (10)

Storage and stability

Telmisartan is hygroscopic and requires protection from moisture. It should be stored at room temperature, 15 to 30°C (59 to 86°F). Moreover, telmisartan suffers discoloration after xenon light irradiation, and therefore it should be protected from direct sunlight. The active substance is stable in alkaline media but decomposes under acidic conditions. Decomposition products are not detected during accelerated and long-term testing studies. (10, 11)

2. OBJECTIVES

The objective of this final degree project is to conduct a comprehensive bibliographic study on Telmisartan 40 mg tablets, focusing on its pharmacological, pharmacokinetic, and pharmaceutical properties. The study also aims to explore formulation challenges and propose an alternative formulation to improve solubility and bioavailability.

Key objectives include:

- Analyze the pharmacodynamic and pharmacokinetic properties of Telmisartan, evaluating its therapeutic indications, mechanism of action, and clinical applications.
- Identify the challenges associated with the low aqueous solubility of Telmisartan and its impact on bioavailability.
- Review existing solubility enhancement techniques and select the most effective strategy for improving Telmisartan dissolution and absorption.

Based on the results obtained in the bibliographic study, the proposed objectives are:

- Develop an alternative pharmaceutical formulation using solid dispersion technology with PEG 6000, based on recent scientific research.
- Propose a detailed industrial manufacturing process, including preparation, blending, compression, and quality control steps, ensuring compliance with European Pharmacopoeia standards.

- Design an environmentally sustainable packaging solution, incorporating eco-friendly materials and aligning with Spain's SIGRE recycling system.

3. MATERIALS AND METHODS

This final degree project corresponds to a bibliographic research study on Telmisartan 40 mg tablets, focusing on their pharmacological properties, formulation strategies, industrial manufacturing, and environmental impact. For the research and selection of scientific literature, several official bibliographic databases were consulted, including PubMed, SCOPUS, and CERCABIB. CERCABIB was the primary resource due to its access to a wide range of scientific publications available through the University of Barcelona.

To conduct the bibliographic search, a Boolean search strategy was applied using keywords such as "Telmisartan AND solubility enhancement" and "Telmisartan AND solid dispersion", retrieving relevant studies on the improvement of Telmisartan's bioavailability and formulation techniques. For the organization and citation of references, the Mendeley reference manager was used.

Additionally, Microsoft Word was used for documentation, while the packaging design proposal was created using standard design tools and Canva to ensure clarity and alignment with sustainability principles.

4. RESULTS AND DISCUSSION

4.1. Telmisartan mechanism of action

Telmisartan is an orally active angiotensin II AT1 receptor antagonist. It has the highest affinity for the AT1 receptor among commercially available ARBs and has minimal affinity for the AT2 receptor. By selectively blocking the binding of angiotensin II to the AT1 receptors telmisartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II. The reduction in plasma aldosterone levels is a key effect of Telmisartan, which helps in reducing sodium and water retention, further contributing to the antihypertensive effects. The reduction in aldosterone secretion not only lowers blood pressure but also decreases the risk of cardiovascular remodeling, heart failure, and renal damage, which are common complications in hypertensive patients. (13)

Telmisartan does not exhibit any partial agonist activity at the AT1 receptors and has minimal affinity for AT2 receptors, which is found in many tissues, have not been associated with cardiovascular homeostasis. In vitro binding studies confirm that Telmisartan has no relevant affinity for other receptors, nor does it inhibit human plasma renin. Unlike ACE inhibitors, Telmisartan does not affect the angiotensin-converting enzyme (ACE), nor does it interact with renin or other hormone receptors, or ion channels involved in the regulation of blood pressure and sodium homeostasis. (13)

In hypertensive patients, blockade of angiotensin II AT1 receptors results in two-to-three-fold increase in plasma renin and angiotensin II plasma concentrations. Telmisartan's long-lasting binding to the AT1 receptor ensures continuous inhibition of angiotensin II's vasoconstrictor and aldosterone-secreting effects, offering consistent blood pressure control over an extended period. (3, 13)

New studies suggest that telmisartan may also have PPARγ agonistic properties that could potentially confer beneficial metabolic effects, as PPARγ is a nuclear receptor that regulates specific gene transcription, and whose target genes are involved in the regulation of glucose and

lipid metabolism, as well as anti-inflammatory responses. These properties could also confer metabolic benefits that are currently being explored in clinical trials. (3)

4.2. How telmisartan differs from other ARBS

Telmisartan is a unique angiotensin II receptor blocker (ARB) due to its distinct pharmacokinetic and pharmacodynamic properties. Compared to other ARBs, Telmisartan exhibits a longer half-life, partial peroxisome proliferator-activated receptor gamma (PPAR-γ) agonism, and higher lipophilicity, which contribute to its superior efficacy in blood pressure control, metabolic benefits, and organ protection. (13)

Telmisartan has the longest half-life (24 hours) among commercially available ARBs, allowing for once-daily dosing with sustained antihypertensive effects. In contrast, other ARBs such as Losartan (6 hours), Valsartan (9 hours), Irbesartan (11-15 hours), Olmesartan (13 hours), or Candesartan (9-12 hours) have shorter durations, often leading to fluctuations in blood pressure throughout the day and requiring more frequent dosing or leading to suboptimal coverage at the end of the dosing interval. (3, 14)

This extended half-life ensures a stable 24-hour blood pressure reduction, reducing the risk of early morning hypertension surges, that are linked to increased cardiovascular risk. (14)

Unlike other ARBs, Telmisartan exhibits partial agonist activity on peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor involved in glucose and lipid metabolism, inflammation, and insulin sensitivity. (3)

This property confers additional metabolic benefits, making Telmisartan especially advantageous for hypertensive patients with type 2 diabetes or metabolic syndrome. The effects of PPAR-γ activation include:

- Improved insulin sensitivity, reducing the risk of type 2 diabetes progression.
- Anti-inflammatory effects, contributing to cardiovascular protection.
- Lipid metabolism modulation, potentially reducing triglycerides and increasing HDL cholesterol levels.

Among clinically used ARBs, Telmisartan is the only one with significant activation of PPAR-γ, making it unique in its dual antihypertensive and metabolic benefits, as studies confirm that other ARBs lack significant PPAR-γ activity. (15,16)
Telmisartan is the most lipophilic ARB, allowing better tissue penetration and higher intracellular concentrations, which enhances its cardiovascular and renal protective effects. (Table 1)

Due to its high lipophilicity, Telmisartan can efficiently cross cell membranes, allowing for greater drug accumulation in key target organs such as the heart, kidneys, and vasculature. This characteristic enhances its end-organ protective effects, making it potentially more effective than other ARBs in preventing organ damage. Additionally, studies suggest that Telmisartan is associated with greater cardiovascular and renal benefits, particularly in patients suffering from diabetes and hypertension, further reinforcing its role in long-term cardiovascular protection. (12,17)

Telmisartan is the only ARB indicated for the reduction of cardiovascular (CV) morbidity in patients with manifest atherothrombotic cardiovascular disease (CVD), based on the results of the ONTARGET study. (17)

It has shown a similar reduction in the composite endpoint of CV death, myocardial infarction (MI), stroke, or hospitalization due to heart failure (HF) to that of the active comparator ramipril. The TRANSCEND study, while it failed to reach the composite primary endpoint, showed that telmisartan did reduce hospitalizations for CV reasons, and left ventricular hypertrophy (LVH),

and fewer patients had the combination of macrovascular and microvascular events plus microalbuminuria. In addition, a combined analysis with data from PRoFESS showed a significant benefit of telmisartan on CV death as well as MI and stroke. (18)

Table 1: Comparison of Angiotensin II Receptor Blockers (ARBs) Based on Pharmacokinetic and Pharmacodynamic Properties (3)

	Biological Half-Life (hrs)	Protein Binding (%)	Bioavailability (%)	Time to Peak Plasma Concentration (Tmax, hrs)	Renal/Hepatic Clearance (%)	Volume of Distribution (L)	PPAR-γ Activation
Telmisartan	24	>99	42 – 58	0.5 - 1	1/99	500	Partial agonist
Valsartan	6	95	25	2 - 4	30/70	17	No significant activation
Losartan	2	98.7	33	1	10/90	34	No significant activation
Olmesartan	14 – 16	99	29	1–2	40/60	17	No significant activation
Candesartan	9	99	15	3 - 4	60/40	0.13	No significant activation

4.3. Pharmacokinetics (ADME) of Telmisartan

Pharmacokinetics describes how a drug is absorbed, distributed, metabolized, and eliminated from the body. Understanding these properties is crucial for optimizing dosing regimens, predicting drug interactions, and ensuring therapeutic efficacy. Telmisartan has distinct pharmacokinetic characteristics that differentiate it from other ARBs, particularly in its absorption, distribution, metabolism, and elimination profiles. (12)

4.3.1. Absorption

Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose-dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively.

The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range of 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of 24 hours. Trough plasma concentrations of telmisartan with once-daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing. (19)

4.3.2. Distribution

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding. (19)

4.3.3. Metabolism and Elimination

Telmisartan is minimally metabolized by conjugation to form a pharmacologically inactive acyl-glucuronide. The glucuronide of the parent compound is the only metabolite identified in human plasma and urine, representing approximately 11% of the measured radioactivity in plasma after a single dose. Cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan. Following either intravenous or oral administration, most of the administered dose (>97%) is eliminated unchanged in feces via biliary excretion, independent of the route of administration. In human feces, only the parent compound is found. The drug undergoes saturable first-pass elimination in the gastrointestinal tract, with the fraction not conjugated to glucuronic acid taken up systemically and predominantly eliminated by the liver. The liver's capacity for telmisartan uptake is high but saturable, and doses greater than 40 mg result in high, non-proportional systemic concentrations. Since no data exists for patients with cholestasis, telmisartan is contraindicated in individuals with biliary obstructive disorders. (19)

Renal elimination of telmisartan is minimal. Only small amounts are excreted in urine, with 0.91% of total radioactivity eliminated after intravenous administration and 0.49% after oral administration. The main metabolite excreted in urine is glucuronidated telmisartan, while only 6% of total urinary activity corresponds to unchanged telmisartan, accounting for 0.06% of the total administered dose. (19)

Telmisartan is highly bound to plasma proteins (99.7%), with 99.9% of it bound to serum albumin. Total plasma clearance is greater than 800 mL/min, and both terminal half-life and total clearance appear to be independent of dose. (3)

4.3.4. Factors influencing pharmacokinetics

Telmisartan exhibits nonlinear pharmacokinetics due to hepatic uptake saturation and AT1-receptor binding saturation, especially at lower doses. A TMDD-PBPK model identified OATP1B3-mediated hepatic uptake as a key factor, with albumin significantly enhancing telmisartan transport into hepatocytes. Figure 4 demonstrates that 4.5% human serum albumin (HSA) reduces the cell-to-medium ratio, confirming albumin-mediated uptake. Sensitivity analysis revealed that Km and OATP1B3 influence AUC and Cmax at all doses, while AT1 receptor binding affects lower doses. Additionally, genetic polymorphisms impact pharmacokinetics, as shown in (Figure 5), where SLCO1B3 and UGT1A3 mutations alter drug distribution and clearance, leading to increased exposure. The study confirms that hepatic transport, albumin binding, and genetic variability are critical determinants of telmisartan's nonlinear pharmacokinetics, influencing its absorption, distribution, and elimination. Nonlinear behavior results in disproportionate increases in systemic exposure at higher doses. Understanding these factors is crucial for optimizing telmisartan dosing in different patient populations, including those with genetic variations. (21)

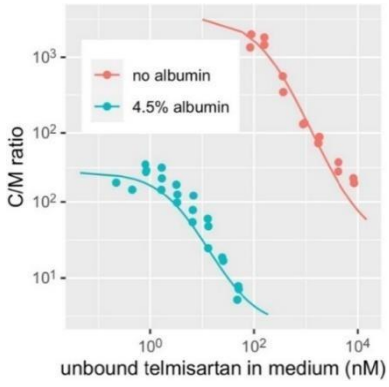

Figure 4: Concentration-dependent uptake study of telmisartan. (21)

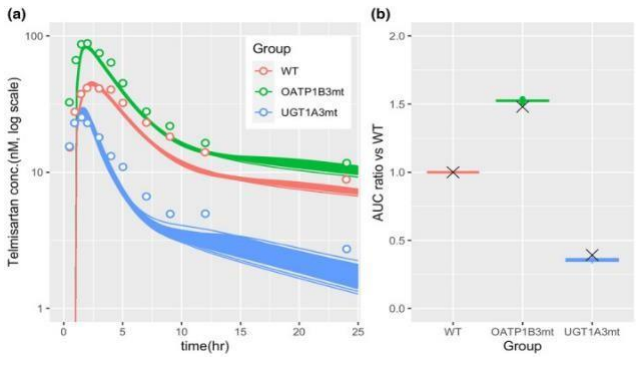

Figure 5: Simulation of telmisartan 40mg P.O. in SLCO1B3 homozygous mutation population. (21)

4.3.5. Special populations

Pediatric: Telmisartan pharmacokinetics have not been investigated in pediatric patients.

Geriatric: The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65. (19)

Gender: Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Renal Insufficiency: No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration. (19)

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%. (19)

4.4. Pharmacodynamics

Pharmacodynamics is the study of how drugs interact with the body to produce therapeutic effects and the study of the biochemical, physiologic, and molecular effects of drugs on the body and involves receptor binding (including receptor sensitivity), post receptor effects, and chemical interactions.

Pharmacodynamics, with pharmacokinetics, helps explain the relationship between the dose and response (the drug's effects). The pharmacologic response depends on the drug binding to its target and the concentration of the drug at the receptor site influences the drug's effect.

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak with approximately 40% inhibition persisting for 24 hours. In hypertensive patients with normal renal function, no clinically significant effects on renal plasma flow, filtration fraction, or glomerular filtration rate were observed. In multiple dose studies in hypertensive patients, telmisartan had no adverse effects on renal function as measured by serum creatinine or blood urea nitrogen. (19)

The antihypertensive effects of telmisartan were demonstrated in 6 placebo-controlled clinical trials, in a total of 1773 patients, 1031 of whom were treated with telmisartan. Upon initiation of antihypertensive treatment with telmisartan, blood pressure was reduced after the first dose and there was a gradual increase in the antihypertensive effect during continued treatment for ≤12 weeks, with most of the increase occurring during the first month. Onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. (19)

The magnitude of blood pressure reduction from baseline, after placebo subtraction, was on average (systolic blood pressure SBP/ diastolic blood pressure DBP) -11.3/-7.3 mmHg for telmisartan 40 mg once daily, and -13.7/-8.1 mmHg for telmisartan 80 mg once daily. Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returned to baseline values over a period of several days. During long-term studies (without placebo control) the effect of telmisartan appeared to be maintained for ≥1 year. For those patients treated with telmisartan 80 mg once daily who required additional blood pressure reduction, the addition of a low dose of hydrochlorothiazide (12.5 mg) resulted in incremental blood pressure reductions of -9.4/-7.0 mmHg. The antihypertensive effect of once-daily telmisartan (40-80 mg) was similar to that of once-daily amlodipine (5-10 mg), atenolol (50-100 mg), enalapril (5-20 mg) and lisinopril (10-40 mg). There was essentially no change in heart rate in telmisartan-treated patients in controlled trials. In clinical trials with post-dose in-clinic monitoring, no excessive blood pressure lowering peak effect was observed even after the first dose, and the incidence of symptomatic orthostasis was very low (0.04%). With automated ambulatory blood pressure monitoring, the 24-hour trough-to-peak ratio for telmisartan was determined to be at least 80% for both systolic and

diastolic blood pressure. The antihypertensive effect of telmisartan is not influenced by patient age, weight, or body mass index. (22, 23)

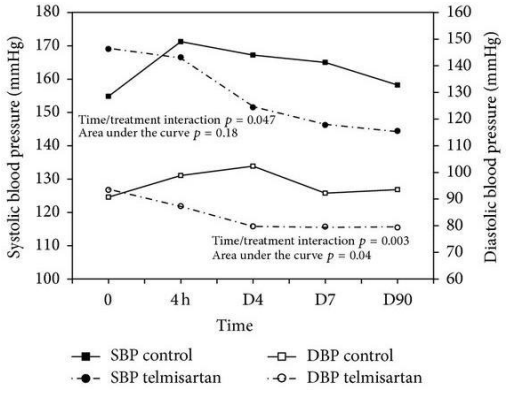

Figure 6: The effect of telmisartan on systolic and diastolic blood pressure over time. (24)

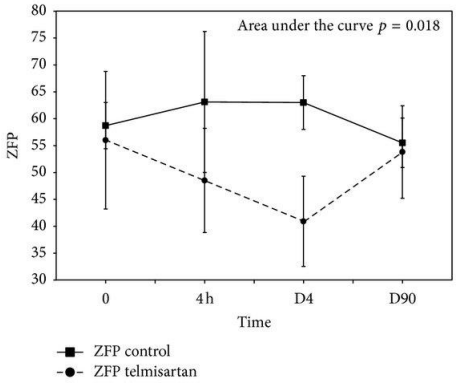

Figure 7: The effect of telmisartan on zero filling pressure (ZFP) over time. (24)

Telmisartan significantly reduces both systolic blood pressure (SBP) and diastolic blood pressure (DBP) over 90 days, as shown in Figure 6 (24). SBP decreases from ~160 mmHg to below 140 mmHg ($p = 0.047$), while DBP drops from ~110 mmHg to below 90 mmHg ($p = 0.003$). The DBP reduction shows a statistically significant area under the curve ($p = 0.04$), confirming the drug's sustained antihypertensive effect. (24)

Telmisartan significantly reduces zero-filling pressure (ZFP), an indicator of preload, from day 4 to day 90 ($p = 0.018$). The control group shows stable ZFP throughout the study (Figure 7). The area under the curve analysis confirms the significant reduction in ZFP in the telmisartan group, highlighting its efficacy in reducing cardiac preload and supporting its cardioprotective effects. (24)

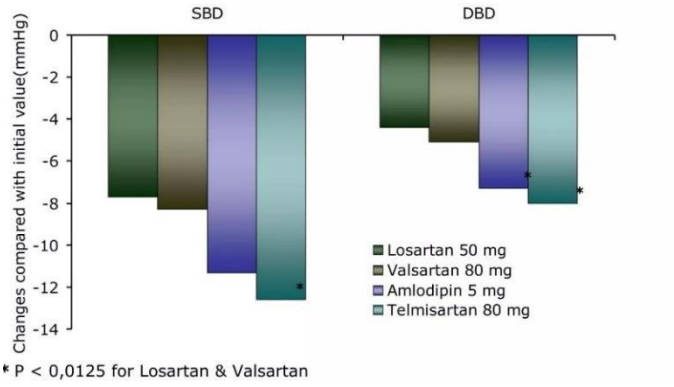

Figure 8: Antihypertensive efficacy over 24 hours - ABPM comparison. (25)

Telmisartan shows the most significant and consistent reduction in both systolic and diastolic blood pressure (SBD and DBD) over 24 hours (Figure 8). The reduction is statistically significant ($P < 0.0125$) compared to Losartan and Valsartan, highlighting its prolonged efficacy and suitability for once-daily dosing. Telmisartan exhibits superior receptor affinity and prolonged blockade, making it highly effective in long-term hypertension management. (25)

4.5. Dose-dependent effects

Dosage must be individualized. The usual starting dose of telmisartan tablets is 40 mg once a day. Blood pressure response is dose-related over the range of 20 to 80 mg. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. (19)

The antihypertensive effects of telmisartan have been demonstrated in six principal placebo-controlled clinical trials, studying a range of 20 to 160 mg; one of these examined the antihypertensive effects of telmisartan and hydrochlorothiazide in combination. (26)

Following once-daily administration of telmisartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure. (26)

With cessation of treatment with telmisartan tablets, blood pressure gradually returned to baseline values over a period of several days to one week. During long-term studies (without placebo control) the effect of telmisartan appeared to be maintained for up to at least one year. (19)

A study evaluating various doses of telmisartan (20 mg to 160 mg) found that all doses significantly reduced blood pressure compared to placebo. However, no significant linear trend in blood pressure reduction was evident among the different telmisartan doses, suggesting a plateau effect beyond certain dosages. This means that increasing the dose (20 mg → 40 mg → 80 mg → 160 mg) leads to greater blood pressure reduction, but beyond 160 mg, the effect plateaus. (26)

4.6. Therapeutic indications and clinical uses

Telmisartan is an angiotensin II receptor blocker (ARB) widely utilized in clinical practice for its efficacy in managing various cardiovascular and metabolic conditions.

4.6.1. Primary indications

- **Hypertension:**

Telmisartan is primarily indicated for treating essential hypertension in adults. It works by selectively blocking the angiotensin II type 1 (AT1) receptor, which reduces systemic vascular resistance and lowers blood pressure. Clinical trials have shown that telmisartan provides sustained 24-hour blood pressure control with once-daily dosing, reducing the risk of cardiovascular events like strokes and myocardial infarctions. Telmisartan has a tolerability profile similar to placebo and is as effective as other major antihypertensive agents in lowering blood pressure. Compared to lisinopril, it is associated with a significantly lower incidence of dry, persistent cough, making it a useful option for patients with hypertension. (19)

- **Cardiovascular Risk Reduction:**

Cardiovascular risk refers to the probability of experiencing cardiovascular events such as heart attack, stroke, or heart failure, influenced by factors like hypertension, hyperlipidemia, smoking, and diabetes.

Beyond its antihypertensive properties, telmisartan is approved for reducing the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years or older who are at high risk for such events and are unable to take ACE inhibitors. This includes individuals with a history of coronary artery disease, peripheral arterial disease, stroke, or diabetes mellitus with end-organ damage. (19)

The ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study is a large comparative trial that evaluated the efficacy of telmisartan, an angiotensin-receptor blocker (ARB), versus ramipril, an established angiotensin-converting enzyme inhibitor (ACEI), in patients with vascular disease or high-risk diabetes. The study demonstrated that telmisartan was non-inferior to ramipril in reducing both fatal and nonfatal cardiovascular events, providing strong evidence for its cardiovascular protection. (19, 27)

ONTARGET is considered a high-quality noninferiority trial and is one of the largest published studies comparing ARBs and ACEIs. However, the combination of telmisartan and ramipril resulted in more adverse effects without any additional benefits. These factors suggest that while telmisartan offers cardiovascular protection comparable to ramipril, its combination with ramipril may not provide added benefit and could increase the risk of adverse effects. (27)

Elevated blood pressure in the early morning is associated with increased cardiovascular risk. It is crucial that antihypertensive medication controls blood pressure to minimize this risk at this time. Unfortunately, some antihypertensives given once daily in the morning may not fulfil this requirement and may place the patient at increased risk. The ARB with the longest half-life is telmisartan. Its potential to reduce blood pressure in the risky early morning hours has been demonstrated in numerous clinical studies using ABPM. Also, of particular importance is the fact that telmisartan has been shown to reduce the early morning blood pressure surge. (28)

The chart (Figure 9) illustrates blood pressure changes over 24 hours, showing a natural decline during sleep (2:00 to 4:00) due to lower metabolic demand. Upon waking (4:00 - 6:00), blood pressure sharply rises due to sympathetic nervous system activation. Blood pressure remains elevated throughout the day, with fluctuations influenced by activity, stress, and other factors.

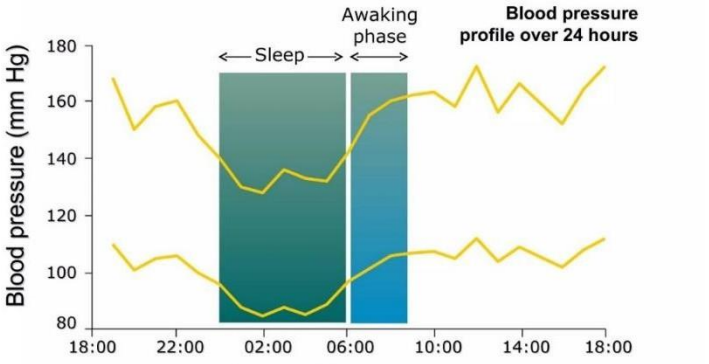

Figure 9: Blood Pressure at Early Morning (29)

The morning surge in blood pressure is significant in hypertension management, as it is linked to an increased risk of cardiovascular events like strokes and heart attacks. (29)

The chart (Figure 10) highlights the correlation between blood pressure changes and cardiovascular events (stroke and myocardial infarction) during the early morning hours. Stroke incidence (yellow line) and myocardial infarction (blue line) both show a significant increase between 4:00 and 10:00, coinciding with a sharp rise in blood pressure.

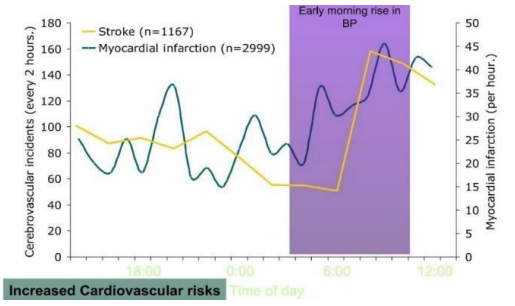

Figure 10: Events at Early Morning (30)

This surge in blood pressure during the awakening phase plays a key role in triggering cardiovascular events. Stroke remains stable overnight but peaks in the morning, while heart attacks also rise dramatically. Antihypertensive treatments like Telmisartan, which provide sustained blood pressure control, are crucial for preventing these risks. (30)

4.6.2. Secondary indications

- **Diabetic nephropathy**

Diabetic nephropathy is a progressive kidney disease caused by long-term diabetes, leading to glomerular damage and impaired kidney function. It presents with proteinuria and

declining GFR and can progress to ESRD if untreated. Early detection and management of blood glucose and blood pressure are essential to slow progression. Telmisartan, though not universally approved for this indication, has shown potential benefits in managing diabetic nephropathy, particularly in type 2 diabetes with renal impairment. By inhibiting angiotensin II, it may reduce intraglomerular pressure and proteinuria, slowing disease progression. Studies suggest its reno-protective effects are comparable to other ARBs. (31)

Current treatment focuses on controlling blood glucose and blood pressure to prevent disease progression. ARBs, especially in early microalbuminuria, improve blood pressure control and provide reno-protection beyond their antihypertensive effects. (31)
Telmisartan's additional PPAR-γ agonistic property enhances insulin sensitivity, reduces renal inflammation, and protects against kidney damage. It helps reduce insulin resistance and glucose intolerance, preventing albuminuria, glomerulosclerosis, and renal fibrosis, offering dual benefits in managing blood glucose and blood pressure. (31)

Renal dysfunction can be regarded as a continuum that extends from endothelial dysfunction to microalbuminuria, macroalbuminuria, end-stage renal disease and ultimately to death. All stages of this continuum are associated with progressively increasing cardiovascular risk. Preventing the development and progression of kidney disease requires rigorous management of blood pressure. Due to the important role of the renin-angiotensin system in the pathogenesis of diabetic renal disease, agents that inhibit this system are recognized as first-line therapy. Telmisartan benefits all stages of diabetic kidney disease in type 2 diabetes, improving endothelial function in normoalbuminuria, delaying progression in microalbuminuria, and reducing proteinuria in macroalbuminuria. Its effectiveness is comparable to ACE inhibitors but with better tolerability. Telmisartan outperforms losartan in protein excretion and is similar to valsartan. These effects support its use in patients with microalbuminuria or overt diabetic nephropathy. (32)

- **Heart Failure**

Heart failure (HF) is a clinical syndrome characterized by the heart's inability to pump blood effectively, resulting in inadequate tissue perfusion and congestion. It commonly arises from conditions such as coronary artery disease, hypertension, or cardiomyopathy. Patients typically present symptoms of fluid retention, dyspnea, and exercise intolerance, with varying degrees of severity depending on the underlying pathology. (33)

Telmisartan is sometimes utilized off-label in managing heart failure, particularly in patients intolerant to ACE inhibitors. Its role in heart failure management stems from its ability to modulate the renin-angiotensin-aldosterone system (RAAS), thereby reducing afterload and preload on the heart. Clinical studies have demonstrated that telmisartan can improve exercise capacity and reduce hospitalization rates in heart failure patients, although it is essential to monitor renal function and potassium levels during therapy. (33)

A randomized, double-blind, placebo-controlled trial with 212 HFpEF patients assessed Telmisartan's effects over 24 weeks. The study found significant improvement in the E/A ratio, indicating better diastolic function. Telmisartan also reduced left ventricular mass and improved LV remodeling, suggesting benefits for heart structure. Patients on Telmisartan had fewer heart failure-related hospitalizations, though the observed trend in improved exercise capacity was not statistically significant. The drug was well-tolerated, with no significant differences in adverse events compared to placebo. While Telmisartan may help manage HFpEF, larger, long-term studies are needed to confirm its effects on mortality and quality of life. (33)

- **Metabolic syndrome and insulin resistance**

Metabolic syndrome is a group of risk factors, including insulin resistance, central obesity, hypertension, and dyslipidemia, that increase the risk of cardiovascular disease and type 2

diabetes. Insulin resistance impairs the body's ability to respond to insulin, leading to elevated blood glucose levels and further metabolic disturbances. (13)

Telmisartan possesses unique properties among ARBs due to its partial agonism of peroxisome proliferator-activated receptor-gamma (PPAR-γ). This activity influences glucose and lipid metabolism, potentially improving insulin sensitivity and exerting beneficial effects on lipid profiles. Clinical trials have suggested that telmisartan may reduce insulin resistance and have favorable effects on glycemic control, making it a therapeutic consideration in patients with metabolic syndrome. (13)

Telmisartan's unique partial activation of peroxisome proliferator-activated receptor gamma (PPARγ) sets it apart from other angiotensin II type 1 receptor blockers (ARBs), enhancing insulin sensitivity while exerting anti-inflammatory and anti-oxidative effects. This dual action positions it as a promising "cardiometabolic sartan" for targeting both diabetes and cardiovascular disease in hypertensive patients. Additionally, studies indicate that telmisartan significantly reduces all-cause mortality, cardiovascular death, and hospital admissions for heart failure in hemodialysis patients with left ventricular ejection fraction (LVEF) ≤40%, even when added to standard therapies. (13)

4.6.3. Combination therapy

Telmisartan is available in fixed-dose combinations with other antihypertensive agents, including hydrochlorothiazide and amlodipine. These combinations are particularly useful for patients who require multiple medications to control their blood pressure effectively.

Combination with Hydrochlorothiazide:

The combination of Telmisartan and hydrochlorothiazide (a thiazide diuretic) is effective in patients whose blood pressure is inadequately controlled by Telmisartan alone. This combination works synergistically to reduce blood volume and lower blood pressure.

Telmisartan is an angiotensin-II receptor blocker effective in reducing blood pressure in hypertension. Many patients require combination therapy, and telmisartan is available with hydrochlorothiazide (HCTZ) in fixed doses (40 mg/12.5 mg, 80 mg/12.5 mg). (32)

Clinical trials using ambulatory blood pressure monitoring showed telmisartan/HCTZ provides greater reductions in blood pressure than monotherapy and increases the percentage of patients reaching target levels. It is more effective than losartan/HCTZ, especially in the early morning hours. Studies show efficacy in elderly, diabetic, and African-American patients. Ongoing research compares telmisartan/HCTZ with valsartan/HCTZ and amlodipine/HCTZ in high-risk populations. (32)

Combination with Amlodipine

In patients who require additional blood pressure lowering, the combination of Telmisartan and amlodipine provides an effective treatment option. Amlodipine further relaxes blood vessels, reducing peripheral resistance and enhancing the blood pressure-lowering effect of Telmisartan. (34)

The combination of telmisartan and amlodipine proved more effective in lowering blood pressure than either drug alone in hypertensive patients. The highest-dose combination achieved the greatest reduction in blood pressure and the highest control rates. Adding telmisartan also reduced the occurrence of peripheral edema, a common side effect of amlodipine. These results highlight the superior efficacy and improved tolerability of telmisartan plus amlodipine, making it a strong option for patients requiring combination therapy. The results demonstrate a dose-dependent reduction in blood pressure, with the greatest effects observed at the highest dose combination. Telmisartan/amlodipine combinations effectively controlled blood pressure across all baseline categories, including severe hypertension. (34)

Telmisartan and Valsartan comparison

The MICADO-II study shows that Telmisartan 80 mg provides a more stable and prolonged systolic blood pressure reduction compared to Valsartan 160 mg (Figure 11), with less fluctuation at later hours. Telmisartan's higher lipophilicity contributes to its longer-lasting effect, making it a better option for patients needing consistent blood pressure control and reducing the risks of morning hypertension surges linked to heart attacks and strokes. (35)

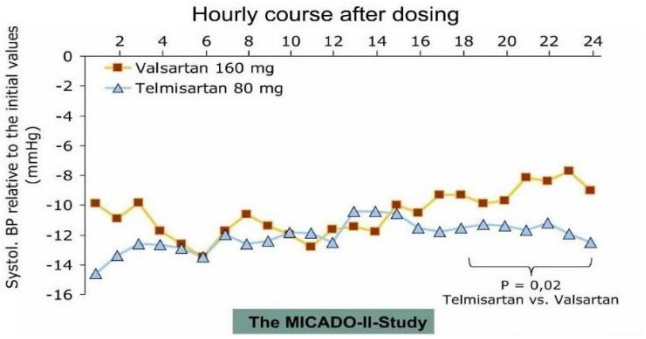

Figure 11: Telmisartan vs. Valsartan – Sustained BP Control Over Time (35)

Telmisartan and Ramipril comparison

The PRISMA-II study (Figure 12) shows Telmisartan 80 mg provides more sustained blood pressure reduction than Ramipril 10 mg ($p < 0.0001$). Telmisartan maintains stable BP control over 24 hours, reducing cardiovascular risk, while Ramipril shows fluctuations. Its longer half-life makes Telmisartan the preferred option for consistent BP management. (36)

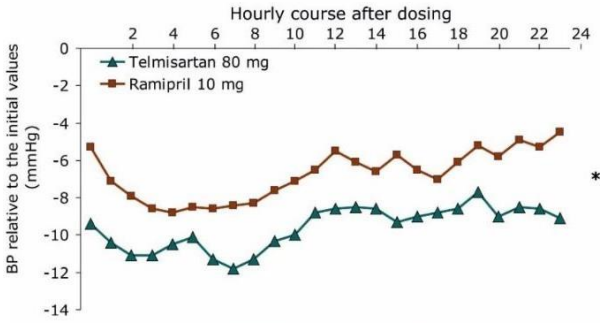

Figure 12: Telmisartan vs. Ramipril – Blood Pressure Reduction Over 24 Hours. (36)

Telmisartan and Amlodipine comparison

Telmisartan (40–120 mg) provides a more stable 24-hour reduction in diastolic blood pressure compared to amlodipine (5–10 mg), with the strongest effect at night (Figure 13). While both drugs significantly lower BP, telmisartan maintains more consistent control, reducing the risk of early morning BP surges linked to cardiovascular events. (37)

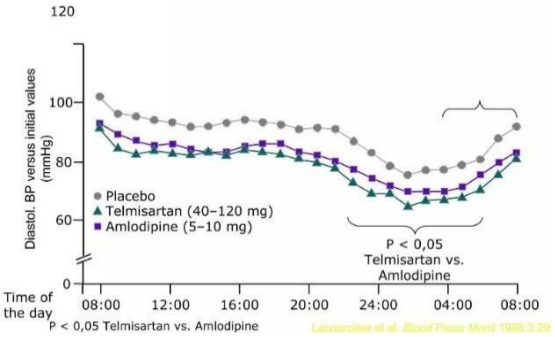

Figure 13: Comparison of Telmisartan and Amlodipine in blood pressure reduction. (37)

Telmisartan's impact on left ventricular hypertrophy (LVH) reduction

Telmisartan (40–80 mg) significantly reduces left ventricular mass index (LVMI) over 12 months, with a clinically meaningful decrease in left ventricular hypertrophy (LVH) by the 12th month ($P < 0.01$) (Figure 14). This suggests telmisartan's cardioprotective benefits, improving cardiac outcomes in hypertensive patients beyond blood pressure reduction. (38)

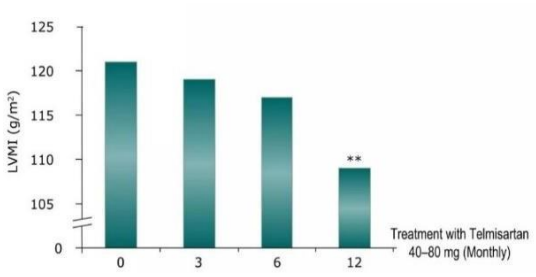

Figure 14: Left ventricular hypertrophy reduction. (38)

Reno-protective effects of Telmisartan

Telmisartan significantly slows the decline in kidney function over five years compared to no treatment. While kidney function deteriorates rapidly in the untreated group, the Telmisartan group maintains higher kidney function levels, especially by year 5 (Figure 15). This highlights Telmisartan's reno-protective benefits, crucial for patients at risk of renal insufficiency, such as those with hypertension or diabetes. (39)

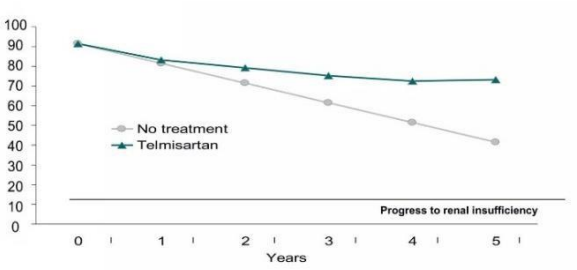

Figure 15: Reno-protective effects of Telmisartan. (39)

4.7. Safety and adverse effects

Telmisartan is generally well tolerated, but like all pharmacological agents, it is associated with potential adverse effects. While most of these effects are mild and manageable, some serious reactions may require medical intervention.

4.7.1. Common side effects

These typically do not require discontinuation of therapy and can often be managed with supportive care.

- Dizziness

Dizziness is a frequently reported side effect, particularly in the initial stages of treatment. This occurs due to the drug's antihypertensive action, which may lead to a transient drop in blood pressure. Patients are advised to rise slowly from a sitting or lying position to minimize the risk of orthostatic hypotension. (19)

- Hyperkalemia

Telmisartan has the potential to increase serum potassium levels, particularly in patients with underlying renal insufficiency or those using potassium-sparing diuretics, potassium supplements, or other medications that elevate potassium levels (e.g., ACE inhibitors). Hyperkalemia can lead to cardiac arrhythmias, making it essential to monitor potassium levels in high-risk patients. (19)

- Hypotension

In some cases, Telmisartan may cause excessive blood pressure reduction, leading to symptoms of hypotension such as lightheadedness, fatigue, and fainting. This is more common in volume-depleted patients, such as those on diuretic therapy or those with heart failure. Adjusting the dosage or ensuring adequate fluid intake can help mitigate this risk. (19)

4.7.2. Rare but serious adverse effects

Although rare, some adverse reactions associated with Telmisartan are severe and require immediate medical attention. (19)

- Renal Impairment

Telmisartan can affect renal function, particularly in patients with pre-existing kidney disease. By reducing glomerular filtration pressure, it may worsen renal function in individuals with bilateral renal artery stenosis or advanced renal impairment. Monitoring renal parameters such as serum creatinine and estimated glomerular filtration rate (eGFR) is recommended during therapy. (19)

- Angioedema

Although more commonly associated with ACE inhibitors, angioedema has been reported in some patients taking ARBs, including Telmisartan. This condition is characterized by severe swelling of the face, lips, tongue, and throat, potentially leading to airway obstruction. Patients with a history of angioedema should avoid ARBs and seek immediate medical attention if symptoms develop.

- Hepatic Dysfunction

Cases of liver enzyme elevation and hepatotoxicity have been reported in some individuals using Telmisartan. Although rare, liver function tests should be conducted in patients with a history of hepatic disease or signs of liver dysfunction. (19)

- Contraindications and Precautions

Before initiating Telmisartan therapy, healthcare providers must assess patients for contraindications and necessary precautions to avoid adverse outcomes. (19)

4.7.3. Contraindications

Pregnancy: Telmisartan is classified as a Category D drug for pregnancy due to its teratogenic potential. It can cause fetal harm, particularly during the second and third trimesters, leading to fetal renal dysfunction, oligohydramnios, and neonatal death.

Bilateral Renal Artery Stenosis: Patients with this condition are at risk of acute renal failure due to decreased renal perfusion. Telmisartan should be avoided in such cases.

Severe Hepatic Impairment: Since Telmisartan is metabolized primarily in the liver, patients with severe hepatic dysfunction should not use this medication. (14, 20)

4.7.4. Precautions

Patients with Diabetes: The combination of Telmisartan with ACE inhibitors or direct renin inhibitors is not recommended in diabetic patients due to the risk of hyperkalemia and renal dysfunction.

Elderly Patients: Older adults may have an increased sensitivity to hypotensive effects, requiring careful dosage adjustments and monitoring.

Concomitant Use of NSAIDs: Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the antihypertensive effects of Telmisartan and increase the risk of renal impairment. Patients taking both medications should be monitored for kidney function and blood pressure control. (18, 20)

4.8. Biopharmaceutics classification system (BCS) and bioavailability considerations of telmisartan

The Biopharmaceutics Classification System (BCS) is a scientific framework used to categorize drugs based on their solubility and permeability, it helps to predict their absorption and bioavailability. It is intended to reduce the need for in vivo bioequivalence studies (it can provide a surrogate for in vivo bioequivalence). (40)

The BCS divides drugs into four classes:

Class I – High solubility, high permeability

Class II – Low solubility, high permeability

Class III – High solubility, low permeability

Class IV – Low solubility, low permeability

Drugs in Class II have good membrane permeability but limited water solubility, making dissolution the rate-limiting step in their absorption. This characteristic significantly influences formulation strategies and regulatory requirements. Unlike BCS Class I drugs, Class II drugs require in vivo bioequivalence studies, as simple in vitro dissolution testing is not sufficient to predict absorption behavior. (40)

There are various methods for enhancing the solubility of drugs from class II and IV, including: Particle size distribution, Formation of the prodrugs /salts, Solid dispersion, Use of co-solvent, Use of surfactant, Hydrotrophy, liquid-solid compact, Microwave-assisted solid dispersion technique, Nanosuspension, Supercritical fluid process. (40)

Physical modifications are also used to enhance solubility, including particle size reduction via micronization, nanosuspensions, and changes in crystal habit, such as polymorphs, amorphous forms, and co-crystallization. Additionally, drugs can be dispersed in carriers like eutectic mixtures, solid dispersions, and solid solutions. (5)

On the other hand, chemical modifications include altering pH, using buffers, derivatization, complexation, and salt formation, all aimed at improving solubility and bioavailability. (80, 90)

Telmisartan belongs to class II and one of the major problems with this drug is its low solubility in biological fluids, which results in poor bioavailability after oral administration. The solubility of Telmisartan in aqueous medium is very low (0.078 mg/ml in water). The absolute bioavailability of Telmisartan is 42-58% and the biological half-life is 24 hours which results in poor bioavailability after oral administration. Poor solubility of Telmisartan leads to poor dissolution and hence variation in bioavailability. Thus, increasing aqueous solubility and dissolution of Telmisartan is of therapeutic importance. (5)

Telmisartan is practically insoluble in water (0.09 mg/mL at pH 7.5) but more soluble at alkaline pH. However, due to its high lipophilicity (log P = 7.7), telmisartan easily crosses biological membranes, ensuring efficient intestinal absorption once dissolved. (5)

The aqueous solubility of Telmisartan is highly pH-dependent (Table 2). It exhibits low solubility in the pH range of 3-7 which is the physiological pH. Since Telmisartan's permeability is high, solubility becomes the main barrier to absorption. Telmisartan is rapidly absorbed from the gastrointestinal tract (GIT) and the maximum absorption was found to be the small intestine where the intraluminal pH was found to be 5-7 to achieve the maximum absorption. (5)

Media	Solubility (µg/ml)
pH 1.2	88.2
pH 4.6	84.9
pH 6.8	36.2
pH 7.4	28.6

Table 2: pH solubility profile of Telmisartan. (41)

4.9. Methods that can be used to enhance solubility for Telmisartan

- **Solid Dispersions**

Solid dispersions are a widely used approach to enhance the solubility, dissolution rate, and oral absorption of poorly water-soluble drugs. In this method, the drug can be distributed molecularly in either crystalline or amorphous particles within an inert matrix. The formation of solid dispersions involves techniques such as melting, solvent evaporation, or a combination of both. These dispersions typically consist of two components: a hydrophilic matrix and a hydrophobic drug, with the matrix existing in either a crystalline or amorphous form. (5)

One important application of solid dispersions is the creation of eutectic systems, where a combination of the drug and a water-soluble carrier solidifies at a lower temperature than its individual components. The eutectic melting point has a well-defined temperature range, and due to its increased surface area, these systems improve drug disintegration and dissolution. This approach is particularly beneficial for lipophilic drugs with low bioavailability, as dissolving them in a solid solution with a highly soluble carrier enhances their absorption. By modifying the properties of the carrier and dispersion particles, an optimal drug release profile can be achieved.

For telmisartan, solid dispersions can be formulated using PEG 4000 and PEG 6000 as carriers in a 1:3 drug-to-carrier molar ratio. The preparation involves mixing the drug and carrier in a recipient placed in a water bath, followed by heating and drying for 24 hours. The resulting solid dispersion showed improved dissolution properties, making it a promising strategy for enhancing telmisartan's bioavailability. (5)

- **Cyclodextrin complexation**

Cyclodextrin (CD) inclusion complexation is a promising approach for improving the solubility and bioavailability of poorly water-soluble pharmaceuticals. This method involves forming host-guest inclusion complexes through weak intermolecular interactions, enhancing drug solubility and stability. Through these interactions, cyclodextrins encapsulate lipophilic drug molecules within their hydrophobic cavity while exposing hydrophilic groups to the surrounding aqueous environment. This results in a water-soluble CD-drug complex with improved pharmaceutical properties. There are various methods to create CD-drug inclusion complexes, including physical mixture, malaxation, and co-evaporation. (5)

In the case of telmisartan, complexation with hydroxypropyl beta-cyclodextrin can be carried out using the physical mixing method. The drug and cyclodextrin are combined in a 1:1 molar ratio and triturated in a mortar and pestle for 30 minutes, ensuring uniform complex formation. This approach enhances telmisartan's solubility and may contribute to better oral bioavailability.

- **Polymeric encapsulation**

The pharmaceutical industry faces a major challenge in developing methods to improve the bioavailability of drugs with low water solubility. Strategies such as particle size reduction and encapsulation with hydrophilic polymers have proven effective in enhancing drug solubility and absorption. Various polymers, including PEG 4000 and PEG 6000, can be used in different ratios to improve the permeability and stability of active ingredients. When enclosed within biodegradable polymers, these formulations contribute to better solubility and, ultimately, enhanced bioavailability. (5)

4.10. Current market formulations of Telmisartan

Telmisartan is available in several formulations on the market. These formulations aim to improve the drug's efficacy and patient compliance. However, Telmisartan faces solubility challenges due to its poor water solubility, which limits its bioavailability.

The following table provides a comprehensive overview of the pharmaceutical formulations of Telmisartan available in the Spanish market. It categorizes the different dosage forms, highlighting their specific characteristics, associated challenges, and potential limitations. Additionally, the table outlines the formulation composition for each dosage form, including a detailed list of excipients used in their manufacturing. (Table 3)

Table 3: Current market formulations of Telmisartan. (42, 43, 44, 45, 46)

Brand Name	Active Ingredients	Dosage Form	Problems and Limitations	List of excipients
Micardis ® Boehringer Ingelheim	Telmisartan	Tablets: 20 mg, 40 mg, 80 mg	Poor dissolution rate due to pH-dependent solubility	Povidone (K25) Meglumine Sodium hydroxide Sorbitol (E420) Magnesium stearate
Telmisartan Teva Pharma ® Teva Pharmaceuticals	Telmisartan	Tablets: 20 mg, 40 mg, 80 mg	Must meet bioequivalence standards with Micardis but may have different excipients affecting dissolution.	Microcrystalline cellulose (Avicel PH 102) Sodium starch glycolate Poloxamers - Meglumine Povidone (PVP K-30) Sorbitol (E420) Magnesium stearate
Kinzalmono ® Bayer AG	Telmisartan	Tablets: 20 mg, 40 mg, 80 mg	Solubility issues and possible variations in disintegration compared to Micardis	Povidone (K25) - Meglumine Sodium hydroxide Sorbitol (E420) Magnesium stearate
Micardis Plus ® Boehringer Ingelheim	Telmisartan + Hydrochlorothiazide (HCTZ)	Tablets: 40/12.5 mg, 80/12.5 mg, 80/25 mg	Limited solubility and potential issues in absorption, HCTZ worsens solubility issues, making formulation more complex.	Lactose monohydrate Magnesium stearate Maize starch - Meglumine Microcrystalline cellulose Povidone (K25) Red ferric oxide (E172) Sodium hydroxide Sodium starch glycollate Sorbitol (E420)
Twynsta ® **Boehringer Ingelheim**	Telmisartan + Amlodipine	Tablets: 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg	Amlodipine (BCS I) dissolves well, but Telmisartan remains solubility-limited	Colloidal anhydrous silica FD&C blue No 1 Ferric oxide black (E172) Ferric oxide yellow (E172) Magnesium stearate - Maize starch - Meglumine Microcrystalline cellulose Povidone K25 Pregelatinized starch Sodium hydroxide Sorbitol

4.11. Enhancing solubility through solid dispersion technology

In this section, will be presented an alternative formulation of Telmisartan aimed at overcoming its solubility limitations, which are a major barrier to its therapeutic efficacy. To address these challenges, a solid dispersion formulation using PEG 6000 as hydrophilic carriers is proposed. Solid dispersions have demonstrated efficacy in enhancing the dissolution rate of poorly soluble drugs by improving wettability, reducing particle size, and transforming the drug into an amorphous form. (47)

This formulation (Table 4) is proposed based on recent research, which highlights its advantages over other solubility enhancement techniques. The use of PEG 4000/6000 (hydrophilic polymers) increases the solubility of Telmisartan by improving its dispersion and conversion into a non-crystalline state. The proposed formulation has the potential to overcome the solubility limitations of Telmisartan, offering a more effective alternative to current marketed formulations. (5)

In this study, two methods of formulation were utilized: the fusion method and the solvent evaporation method. For both methods, PEG-4000 and PEG-6000 were incorporated in different drug-to-polymer ratios, 1:0.5, 1:1, and 1:2. (48)

The fusion method was shown to be more effective than the solvent evaporation method in enhancing the dissolution rate of telmisartan. Among all the formulations, the fusion method with PEG-6000 at a 1:2 ratio achieved the highest drug release of 99.39%, demonstrating superior solubility enhancement compared to other formulations. This was followed by the fusion method with PEG-4000 at a 1:2 ratio, which showed a release of 95.23%. (48)

On the other hand, the solvent evaporation method, although effective, resulted in comparatively lower drug release percentages. Specifically, PEG-6000 at a 1:2 ratio achieved only 76.52% drug release, and PEG-4000 at a 1:2 ratio showed a release of 74.34%. (48)

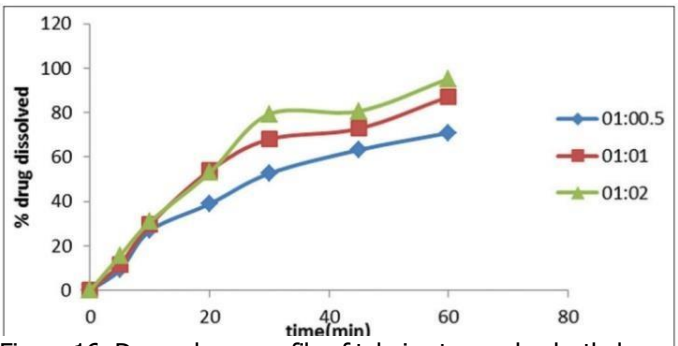

Figure 16: Drug release profile of telmisartan and polyethylene glycol 6000 using fusion method. (48)

The drug release profile (Figure 16) shows improved dissolution with PEG 6000, likely due to enhanced wettability and reduced crystallinity.

Additionally, the first-order release profile (Figure 17) indicates concentration-dependent drug release, supporting better bioavailability. (48)

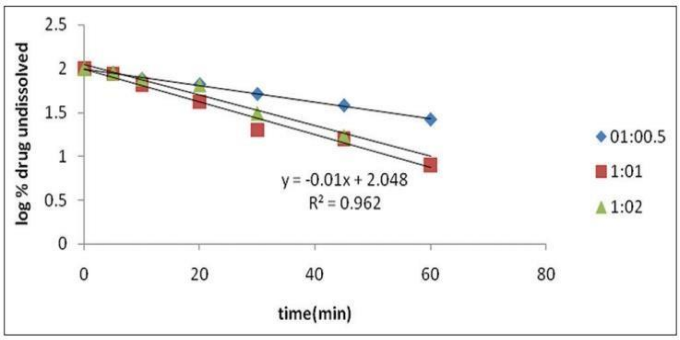

Figure 17: First order drug release profile of telmisartan and polyethylene glycol 6000 using fusion method. (48)

For this reason, the proposed formulation will rely on the fusion method with PEG-6000 at a 1:2 drug-to-polymer ratio, as this combination demonstrated the best results in terms of drug release and solubility enhancement in the study. (48)

Table 4: Proposed alternative formulation of Telmisartan

Materials used	Quantity (mg)	Role of Each Material	Quantity (%)	Quantity (industrial batch) (kg)
Solid dispersion (equivalent to 40 mg)	120 mg	Telmisartan + PEG 6000 (1:2) (fusion method)	60.0%	38.16 kg
Starch	16 mg	Binder and disintegrant	8.0%	4.49 kg
MCC (Microcrystalline cellulose)	20 mg	Filler and binder	10.0%	5.61 kg
Talc	16 mg	Lubricant and anti-adherent.	8.0%	4.49 kg
Magnesium stearate	15 mg	Lubricant for smooth tablet formation	7.5%	4.67 kg
Sodium Starch Glycolate (SSG)	6 mg	Disintegrant	3.0%	1.79 kg
Povidone K25 (PVP K25)	7 mg	Binder and solubility enhancer	3.5%	2.09 kg
Total weight of tablet	200 mg		100%	61.3 kg

List of excipients and their functions:

- **Starch** acts as a binder and disintegrant in tablets, helping them to break apart in the stomach for proper drug release. It also improves the mechanical strength of the tablet, preventing it from crumbling. Typically used at concentrations of 5–10% as a binder and 3–20% as a disintegrant. (49)
- **Microcrystalline Cellulose (MCC)** is used as a filler and binder (10–30%) in tablet formulations, adding bulk and providing structural integrity. It aids in maintaining the stability of the tablet during compression and ensures uniform drug distribution. (49)
- **Talc** serves as a lubricant and anti-adherent in tablet formulations, reducing friction during the compression process. It prevents the tablet from sticking to the machine and ensures smooth tablet formation. Usually used at concentrations of 1–5%. (49)
- **Magnesium stearate** is a lubricant used to reduce friction between the tablet material and the machine during manufacturing. This excipient helps in smooth tablet compression and ensures uniformity in the final product. Typically added at concentration of 0.25–2%.
- **Sodium Starch Glycolate (SSG)** is a disintegrant that helps the tablet break down rapidly upon ingestion. It absorbs water and swells, allowing the active ingredient to be released effectively and enhancing the dissolution rate. Usually used at 2–8%. (49)
- **Povidone K25** acts as a binder, improving the cohesion of the tablet components. It ensures the tablet holds together during manufacturing and enhances the dissolution of the active ingredient in the body. Typically used at concentrations of 2–10%. (49)

4.12. Manufacturing of Telmisartan tablets

To produce a batch with 10,000 boxes of tablets, with each box containing 28 tablets, a total of 280,000 tablets must be manufactured. During the production process, some materials and tablets may be lost due to various factors, including handling, processing, or losses during quality control checks. To compensate for this potential loss, an additional 7% of the total required raw materials and tablets are produced to ensure that the final quantity of tablets is sufficient for

packaging. In the table 3, the quantities listed for the industrial-level production already include the additional 7% to account for material loss during the manufacturing process. (50)

1) Weighing the starting materials

The process begins with weighing all components (API and excipients) to produce a batch with a specific size. Previously, the components must have passed quality controls to meet the expected safety and efficacy. The excipients are weighed using an industrial precision balance and then transferred to the appropriate container. (50)

The **Mettler Toledo industrial precision balance** (ICS689-CC600) (Figure 18) is a high-precision industrial balance designed for accurate weighing of large quantities in pharmaceutical manufacturing. It offers advanced features like automatic calibration, high stability, and is capable of weighing up to 600 grams with exceptional precision, making it ideal for ensuring the correct ratio of ingredients in large-scale formulations. (59)

Figure 18: The Mettler Toledo industrial precision balance (ICS689-CC600) (59)

2) Preparation of solid dispersion

The fusion method is employed to prepare the mixture of Telmisartan and PEG 6000, resulting in a homogeneous solid dispersion that enhances the solubility of the active pharmaceutical ingredient. The first step is to weigh the precise amounts of Telmisartan and PEG 6000. The ratio used is 1:2 (Telmisartan: PEG 6000). PEG 6000 is then heated to its melting point (60-63°C) using a controlled heating source (jacketed mixing container). Once melted, Telmisartan is added to the molten excipient and mixed thoroughly to form a homogeneous solid dispersion. During the fusion method, it is crucial to maintain the temperature just above the melting point of PEG 6000, typically between 65-70°C to ensure the excipient is in a molten state but without overheating, which could degrade the material. Once the fusion process is complete, the mixture is allowed to cool and solidify, resulting in a solid dispersion. This solid dispersion is then ready for further processing to form tablets. (48)

The **jacketed mixing container** (Figure 19) is a stainless-steel vessel designed for precise temperature control in pharmaceutical manufacturing. Its double-walled jacket allows uniform heating or cooling, making it ideal for mixing, melting, and maintaining temperature-sensitive formulations like solid dispersions. (60)

Figure 19: Jacketed Mixing Container (Pharma Hygiene Products) (60)

3) Sieving for particle size uniformity

The solid dispersion and excipients undergo sieving to ensure uniform particle size, which is critical for achieving consistent tablet weight, dissolution rate, and flow properties during compression. Sieving helps eliminate lumps, oversized particles, and aggregates, thereby improving the powder uniformity for further processing. A mesh size of 80–100 (150–180 microns) is typically used. The solid dispersion, along with all excipients, passes through the sieve. (50)
A circular sieve or a vibratory sieve shaker is used, where fine particles pass through, while larger particles are broken down or removed. The **ZEUS circular sieve shaker** is designed for high-precision sieving and particle size analysis, utilizing a circular motion to effectively separate

powders and granules. It is equipped with adjustable settings for vibration speed and time, allowing for consistent results. (Figure 20, Figure 21) (61)

Figure 20: The ZEUS circular sieve shaker (61)

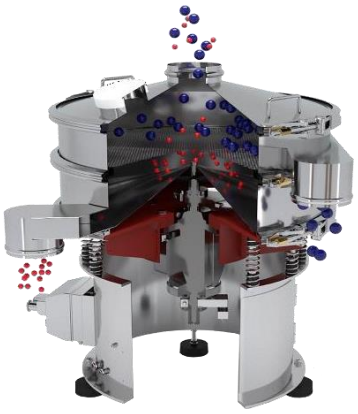

Figure 21: The ZEUS circular sieve shaker (61)

4) Blending with other excipients

The dried solid dispersion of Telmisartan and PEG 6000 is carefully blended with the other excipients, to ensure uniform distribution. This step is crucial for achieving consistent tablet quality and performance. The **V-blender** (Figure 22) is used, as it is suitable for handling large volumes and ensure that the excipients are evenly mixed with the solid dispersion. The typical blending time for a batch of this size (61.3 kg) can range from 10 to 30 minutes. (50)

Figure 22: The V-blender (63)

5) Tablet compression

The blended powder mixture is compressed into tablets using a rotary tablet press through the direct compression method. The rotary press applies controlled force to shape the tablets with specific weight, size, and hardness. Compression parameters such as force, speed, and powder weight are adjusted to achieve the desired tablet characteristics, ensuring proper tablet hardness, disintegration, and dissolution rates. (50)

Fette P Series – F30P (Figure 23) is a double rotary tablet press, ideal for large batch production with flexible adaptability to various requirements. (62)

Figure 23: Fette P Series – F30P (62)

Stages of the rotary tablet press (Figure 24):

- Powder Filling: In this pre-compression stage, the lower punch moves to its lowest position, allowing the die cavity to fill with powder.
- Dosing: Precise dosing ensures uniform tablet weight. The lower punch rises slightly to remove excess powder, which is scraped off to maintain consistency.

- Pre-Compression (Optional): This step removes trapped air to prevent tablet defects. The upper and lower punches apply a preliminary force, but it is not enough to form the final tablet. The pre-compression roller is smaller than the main compression roller.
- Main Compression: The upper punch descends fully, applying the required force to form the tablet.
- Ejection: Once the tablet is formed, the upper punch retracts, and the lower punch rises to eject the tablet from the die. (50)

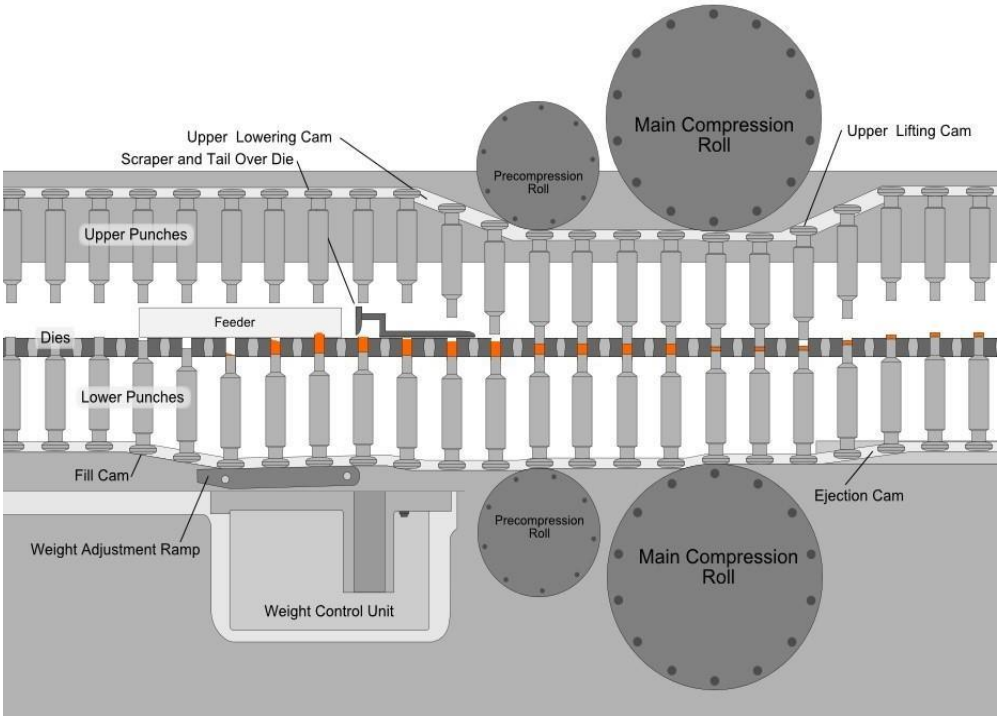

Figure 24: Tablet manufacturing process in an industrial rotary compression machine (5)

It must be verified that the final tablets do not contain metals, which is why there are machines that are used at the end of the process with the capacity to evaluate their content and, if they exceed the limits, reject the tablets. (50)

4.13. Quality controls and specifications

Quality controls for the manufacturing process include both in-process quality control and finished product quality control tests. In-process quality control tests are conducted during production to ensure consistency, while finished product quality control tests evaluate the final tablets' compliance with established standards. Both are carried out in accordance with the European Pharmacopoeia (Ph. Eur.) and good manufacturing practice (GMP) guidelines.

In Directive 2001/83/EC, the sections related to quality control of medicinal products are mainly covered in Articles 46, 47, 48, 50, and 51, which focus on manufacturing, good manufacturing practices (GMP), and batch release requirements. (52)

- Angle of Repose

The angle of repose is determined using a funnel. An accurately weighed quantity of powder is placed in a funnel, with the height adjusted so that the tip of the funnel just touched the apex of the powder cone. The powder is allowed to flow freely onto the surface, and the diameter of the powder cone is measured. The angle of repose is then calculated using the following equation:

$$tan(\boldsymbol{\theta}) = \frac{\boldsymbol{r}}{\boldsymbol{h}}$$

Where h is the height of the cone, and r is the radius of the cone's base.

According to Ph. Eur., the angle of repose for powders used in tablets should typically be between 25° and 40°, which indicates passable flow properties. (36)

- Bulk Density

Apparent bulk density is determined by pouring a weighed quantity of blend into a graduated cylinder and measuring the volume and weight. Bulk density is calculated using the following formula:

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{bulk volume of powder}}$$

The bulk density of various powder sample sizes (10 g) of different ratios of drug and excipients is taken in a graduated cylinder and measured with bulk density apparatus. The bulk density for powders used in tablet formulations should generally be in the range of 0.3–0.6 g/cm³. (50)

- Tapped density

It is determined by tapping a graduated cylinder containing a known amount of powder and measuring the change in volume after tapping. Tapped density for powders used in immediate-release tablet formulations should typically be in the range of 0.4–0.7 g/cm³. (50)

- Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

A Hausner's ratio of 1.2 or less is usually considered an indicator of good flowability for powders used in tablet formulations. (50)

- Compressibility index

The compressibility index (CI) is determined by the difference between bulk density and tapped density. It provides an indication of powder flowability and is calculated as:

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

The compressibility index for tablet powders should generally be in the range of 12–20%. A CI within this range indicates that the powder is suitable for tableting without significant issues related to flow or compression. (50)

- General appearance

The formulated tablets are assessed for their overall appearance, including shape, color, texture, and odor. The tablets should be oblong-shaped, smooth in texture, and white in color. They must not exhibit any manufacturing defects such as picking, sticking, lamination, chipping, capping, or cracking. Any defects may indicate improper processing or contamination. (50)

- Identification

The presence of the active pharmaceutical ingredient (API) in the tablets is confirmed using suitable identification techniques, such as infrared absorption spectrophotometry, which is used to verify the chemical identity of the API. (50)

- Weight variation test

To assess uniformity in tablet weight, a sample of 20 tablets is selected from the batch, and their average weight is determined. The individual tablet weights are then measured, and the percentage variation is calculated.

The formula for weight variation is:

$$\%\,\text{Weight variation} = \frac{\text{average weight of tablet} - \text{weight of each tablet}}{\text{average weight of tablet}}$$

For acceptable quality, the weight variation should remain within the European Pharmacopoeia's standard range for tablets of 200 mg ± 7.5%. Tablets with greater deviations in weight may not meet the required quality standards for consistent dosing. (50)

- Hardness

The hardness test ensures the tablets have enough strength to withstand packaging, shipping, and handling without breaking. Using a Monsanto hardness tester, the force required to fracture the tablet is measured. The recorded values reflect the tablet's hardness. The typical hardness range is between 4–6 kg/cm², ensuring that the tablets are adequately durable for handling. (50)

- Thickness of the tablets

The thickness test is performed using vernier calipers to check the uniformity in tablet thickness, which is essential for correct dosing and packaging. The standard thickness for tablets is between 2.0 mm and 4.0 mm. (50)

- Friability test

The friability test assesses the tablets' resistance to crumbling, an essential factor for tablet durability during handling and transport. In this test, 10 tablets are rotated in a Roche friabilator for 100 revolutions, and the weight loss is calculated. The acceptable weight loss limit is 1.0%, indicating that the tablets have a strong resistance to breaking and crumbling. (50)

- Disintegration test

The disintegration test is performed to assess how quickly the tablets break apart in the digestive tract. Six tablets are placed in the disintegration apparatus, and the basket is lifted after the specified time to check if all six units have disintegrated. Immediate-release tablets should disintegrate within 15 minutes. (50)

- Dissolution test

The dissolution test evaluates the rate and extent at which the active pharmaceutical ingredient (API) is released from the tablet. Immediate-release tablets are considered to dissolve rapidly if 80% of the labeled amount of the drug dissolves within 15 minutes in pH 1.2, 4.0, and 6.8 media.

- Uniformity of dosage units

The uniformity of dosage units test ensures that each tablet contains a consistent amount of the active pharmaceutical ingredient (API). This is assessed through weight variation or content

uniformity tests. This is crucial to maintain the consistency and reliability of the therapeutic dose in each tablet. (50)

- Assay

The assay is performed to determine the actual amount of API present in the tablets. A total of five weighed tablets are powdered, and a portion is dissolved in methanol. The solution is then diluted and analyzed using spectrophotometry at 296 nm. The measured drug content should fall within 95% to 105% of the labeled claim, ensuring that each tablet delivers the correct dose of the active ingredient. (48)

- In Vitro dissolution study

The in vitro dissolution study evaluates the rate and extent of API release using a USP Type 2 apparatus (paddle) at 75 rpm. A dissolution medium of 0.1 N HCl is used, maintained at a temperature of 37 ± 0.5°C. Samples are withdrawn at specified intervals and analyzed spectrophotometrically at 296 nm. For immediate-release tablets, it is required that at least 80% of the drug dissolves within 15 minutes, confirming that the formulation meets rapid dissolution criteria. (48)

- Microbial quality of tablets

The European Pharmacopoeia (Ph. Eur.) sets microbial limits to ensure pharmaceutical tablets, including immediate-release formulations like telmisartan tablets, are free from harmful microbial contamination.

- Total Aerobic Microbial Count (TAMC): $\leq 10^4$ CFU/g
- Total Yeasts and Molds Count (TYMC): $\leq 10^2$ CFU/g
- Specified Pathogens (Absence Required): E. coli (1g), Salmonella spp. (10g), P. aeruginosa (1g), S. aureus (1g), and bile-tolerant Gram-negative bacteria (1g).

Testing follows Ph. Eur. using membrane filtration, plate-count techniques, and enrichment cultures to detect contaminants. (53)

4.14. Safety considerations

Throughout the entire production process, laboratory safety measures are strictly adhered to protect personnel and maintain a safe working environment. Personal protective equipment (PPE) such as gloves, lab coats, and safety goggles are worn at all times to minimize exposure to chemicals. Regular training on safe lab practices is conducted to ensure compliance with safety protocols. (59)

4.15. Packaging (Primary and secondary)

Primary Packaging:

The primary packaging is the first layer of protection for the pharmaceutical product. It is designed to provide a barrier to external elements such as light, moisture, and air, which can degrade the active pharmaceutical ingredient (API).

The choice of materials for primary packaging is critical for maintaining the stability, efficacy, and shelf-life of the product. (54)

Materials used in primary packaging for tablets:

Blister packs:

Blister packs are one of the most commonly used packaging types for tablets. They provide excellent protection against moisture, air, and light, ensuring the stability of the API. The blister cavity is typically made from a combination of PVC (Polyvinyl Chloride) and aluminum foil. (56)

- PVC (Polyvinyl chloride): PVC is a cost-effective and widely used material for the thermoforming of blister packs. It is transparent, allowing for easy inspection of the product. However, PVC alone is not moisture-resistant, so it is often used in combination with aluminum foil. (56)
- Aluminum foil: Aluminum is a perfect barrier material that offers high resistance to light, moisture, and oxygen, protecting the API from environmental degradation. Aluminum foil is often used as the lidding material for blister packs. (56)

Blister packs are sealed by applying heat or pressure, creating individual compartments for each tablet, which makes them convenient for unit-dose applications. Additionally, blister packs offer tamper-evident features, which enhance safety by providing visible proof of tampering. (56)

The secondary packaging includes two blisters, with each blister containing 14 tablets.

Secondary packaging:

Secondary packaging refers to the outer packaging that holds one or more primary packages, providing further protection during storage, handling, and transportation. (57)

It also serves as a means of displaying important product information for the user. Secondary packaging typically involves the use of boxes, cartons, or other sturdy materials that facilitate the distribution and storage of pharmaceutical products. (54)

Materials used in secondary packaging:

Cardboard (Paperboard) boxes

Cardboard or paperboard boxes are widely used for secondary packaging due to their strength, versatility, and cost-effectiveness. These boxes offer physical protection from damage during handling and transportation. (57)

Corrugated cardboard is used for bulk packaging, while solid paperboard is used for individual packaging of smaller quantities. Cardboard is lightweight and provides adequate protection against physical damage. It is also an environmentally friendly option, being recyclable and biodegradable. The weight of the packaging is minimized by reducing its dimensions and thickness, resulting in small packaging with the following dimensions: 12 × 8 × 2.5 cm.

4.16. Design of secondary packaging

The secondary packaging design (Figure 24) should ensure that all mandatory and important product information according to Articles 54 and 59 of Directive 2001/83/EC (55) is displayed clearly, including:

- **Drug Name and Strength:** Telmizan (Each tablet contains 40 mg telmisartan).
- **The national code (CN).**
- **Batch Number and Expiry Date.**
- **Storage Instructions:** Store in the original package in order to protect from moisture.
- **Excipients:** The formulation does not contain any excipients subject to mandatory declaration.
- **Warnings and Contraindications**: Keep out of the sight and reach of children.
- **Barcodes:** Essential for traceability, inventory control, and facilitating easy access to product information during distribution.
- **Regulatory Labels**: including the manufacturer's name and contact details, as well as the country of origin.
- **Recommendation to read the prospectus.**

- **Indication of medicine subject to medical prescription.**
- **SIGRE logo.**
- **Blank space** to be filled in by the pharmacist with important information.
- **Patient Information Leaflet (PIL):** the PIL should be included inside the packaging, providing comprehensive information about the medication, including indications, dosage, and potential side effects. (55)

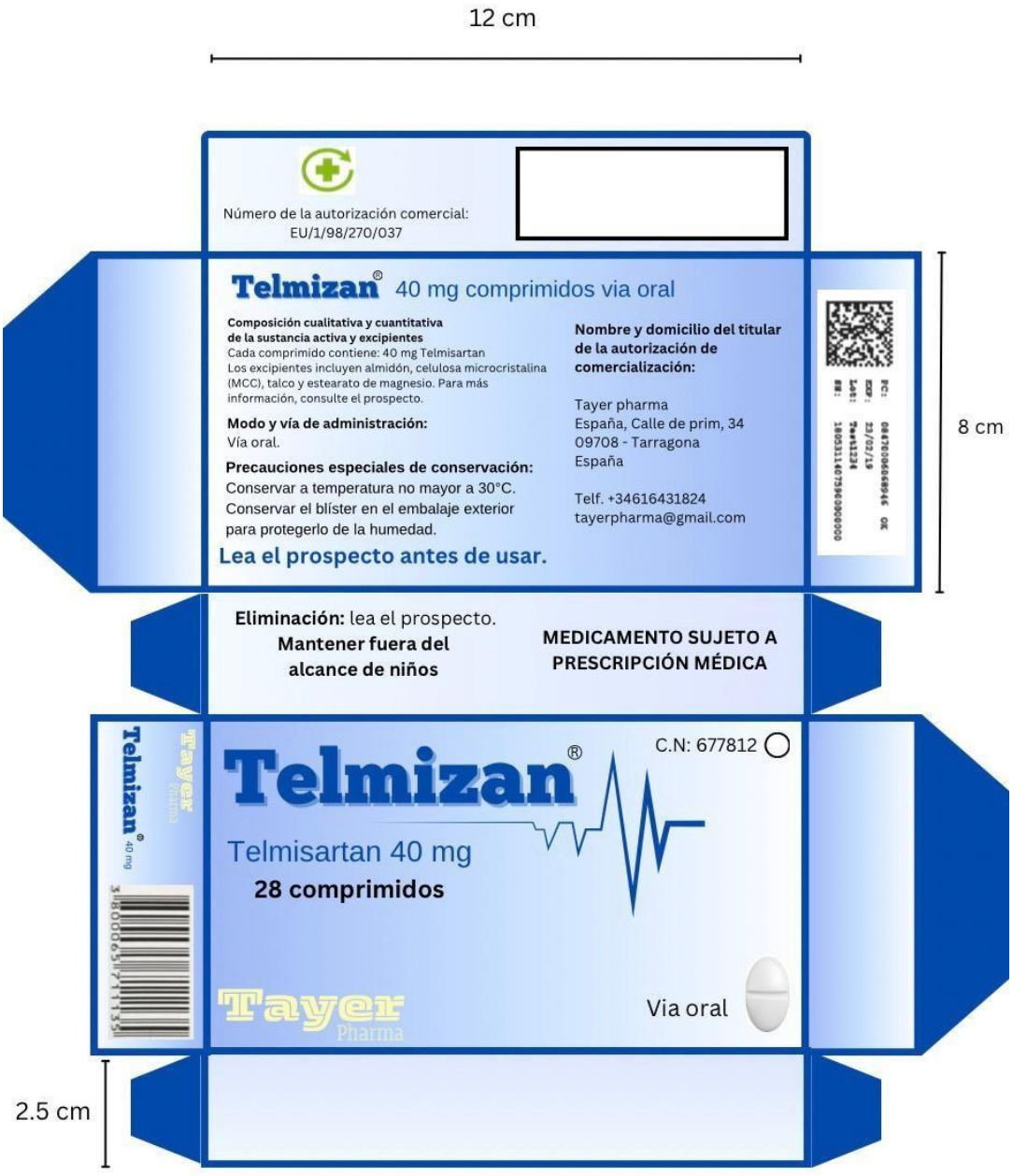

Figure 25: Design of the secondary packaging of Telmizan.

4.17. Environmental management and sustainability in Telmisartan production

Environmental management plays a crucial role in reducing the ecological impact of pharmaceutical products, including Telmisartan. Sustainability is prioritized throughout the entire lifecycle of the drug, from production to packaging. In the production process, the use of sustainable manufacturing practices is key. By adopting energy-efficient technologies, laboratories can reduce their energy consumption, thereby lowering the environmental impact. Additionally, green chemistry principles are applied to minimize the use of harmful solvents and reagents. This results in fewer by-products and a reduction in chemical waste, contributing to an eco-friendlier production process.

The use of recyclable, biodegradable materials helps to reduce waste, ensuring that the packaging does not contribute to long-term environmental harm. Optimizing the size of packaging also reduces the number of raw materials required, leading to a decrease in overall environmental impact. By maintaining high standards in the packaging process, the integrity and safety of the pharmaceutical product are preserved while minimizing resource consumption.

In Spain, the SIGRE (Sistema Integrado de Gestión y Reciclaje de Envases) system plays an essential role in collecting and recycling pharmaceutical packaging. The program facilitates the return of used medication packaging, such as boxes and blister packs, to collection points in pharmacies across the country. These materials are then properly recycled, reducing the environmental burden of pharmaceutical waste. By ensuring that packaging is returned to SIGRE collection points rather than being disposed of in regular waste streams, pharmaceutical companies like those producing Telmisartan contribute to responsible recycling practices and environmental conservation. (54)

Furthermore, pharmaceutical manufacturing laboratories are increasingly implementing practices that prioritize environmental sustainability. In addition to energy-efficient equipment, the use of closed-loop systems in the production of Telmisartan helps minimize resource consumption, such as water and raw materials, while ensuring that waste products are properly treated and recycled. These practices contribute to a reduction in the overall ecological footprint of drug manufacturing.

By aligning the production and disposal processes of Telmisartan with environmentally responsible practices, this research supports sustainable development goals (SDG 12: Responsible Production and Consumption), focusing on the reduction of waste and the careful management of resources. Through innovations in both production and packaging, the pharmaceutical industry can contribute to a more sustainable future. (58)

5. CONCLUSIONS

In reference to the objectives established at the beginning of this bibliographic study, the main conclusions are as follows:

1. Telmisartan is a BCS Class II drug (low solubility, high permeability), and its bioavailability is limited by its poor aqueous solubility. Its absolute bioavailability ranges between 42-58%, and it exhibits a pH-dependent solubility profile, being practically insoluble in water but more soluble in alkaline conditions. Its high lipophilicity (log P = 7.7) ensures efficient absorption once dissolved, but the solubility barrier remains the main challenge for oral administration.

2. Solubility enhancement is key to improving the therapeutic efficacy of Telmisartan. Various techniques, including solid dispersions, cyclodextrin inclusion complexes, and polymeric encapsulation, were reviewed in the literature. Based on published studies, the solid dispersion method using PEG 6000 (fusion method, 1:2 drug-to-polymer ratio) was found to be the most effective, achieving a dissolution rate of 99.39%. This method is identified as the optimal solution for enhancing Telmisartan's solubility.

3. A new formulation of Telmisartan using solid dispersion technology was proposed to overcome solubility limitations. This formulation was optimized based on scientific studies demonstrating that PEG 6000 enhances wettability, reduces crystallinity, and improves dissolution behavior. The fusion method was chosen due to its higher efficiency compared to solvent evaporation techniques.

4. A complete manufacturing process was designed for the optimized Telmisartan formulation. The process includes solid dispersion preparation, sieving, blending, direct compression, and quality control testing in compliance with European Pharmacopoeia standards. Pre- and post-compression tests ensure tablet uniformity, mechanical strength, and dissolution characteristics suitable for immediate-release formulations.

5. An environmentally sustainable packaging system was proposed to align with current pharmaceutical industry trends. The primary packaging consists of blister packs using PVC and aluminum foil, ensuring optimal protection against moisture, light, and oxidation. The secondary packaging uses recyclable cardboard with clear regulatory labeling.

6. This research highlights the importance of sustainability in pharmaceutical development. Sustainable practices were integrated into the formulation and packaging, reducing the environmental footprint of Telmisartan production.

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7. ANNEXES

Annex 1

Package leaflet: Information for the user
Telmizan 40 mg tablets
Telmisartan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Telmizan is and what it is used for

Telmizan belongs to a class of medicines known as angiotensin II receptor blockers. Angiotensin II is a substance produced in your body that causes your blood vessels to narrow, thus increasing your blood pressure. Telmizan blocks the effect of angiotensin II so that the blood vessels relax, and your blood pressure is lowered. Telmizan is used to treat essential hypertension (high blood pressure) in adults. 'Essential' means that high blood pressure is not caused by any other condition. High blood pressure, if not treated, can damage blood vessels in several organs, which could lead sometimes to heart attack, heart or kidney failure, stroke, or blindness. There are usually no symptoms of high blood pressure before damage occurs. Thus, it is important to regularly measure blood pressure to verify if it is within the normal range. Telmizan is also used to reduce cardiovascular events (i.e. heart attack or stroke) in adults who are at risk because they have a reduced or blocked blood supply to the heart or legs, have had a stroke, or have high-risk diabetes. Your doctor can tell you if you are at high risk for such events.

2. What you need to know before you take Telmizan

Do not take Telmizan

• if you are allergic to telmisartan or any of the other ingredients of this medicine (listed in section 6).
• if you are more than 3 months pregnant. (It is also better to avoid Telmizan in early pregnancy – see pregnancy section.)

• if you have severe liver problems such as cholestasis or biliary obstruction (problems with drainage of the bile from the liver and gall bladder) or any other severe liver disease.

• if you have diabetes or impaired kidney function and you are being treated with a blood pressure lowering medicine containing aliskiren.

If any of the above applies to you, tell your doctor or pharmacist before taking Telmizan.

3. Warnings and precautions

Talk to your doctor before taking Telmizan if you are suffering or have ever suffered from any of the following conditions or illnesses:

• Kidney disease or kidney transplant.

• Renal artery stenosis (narrowing of the blood vessels to one or both kidneys).

• Liver disease.

• Heart trouble.

• Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).

• Low blood pressure (hypotension), likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to e.g. diuretic therapy ('water tablets'), low-salt diet, diarrhea, or vomiting.

• Elevated potassium levels in your blood.

• Diabetes.

Talk to your doctor before taking Telmizan:

- if you are taking any of the following medicines used to treat high blood pressure:
- an ACE inhibitor (for example enalapril, lisinopril, ramipril), in particular, if you have diabetes-related kidney problems.
- aliskiren.
  Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals. See also information under the heading "Do not take Telmizan".
- if you are taking digoxin.

Talk to your doctor if you experience abdominal pain, nausea, vomiting, or diarrhea after taking Telmizan. Your doctor will decide on further treatment. Do not stop taking Telmizan on your own. You must tell your doctor if you think you are (or might become) pregnant. Telmizan is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section). In case of surgery or anesthesia, you should tell your doctor that you are taking Telmizan. Telmizan may be less effective in lowering the blood pressure in black patients.

Children and adolescents

The use of Telmizan in children and adolescents up to the age of 18 years is not recommended.

Other medicines and Telmizan

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change the dose of these other medications or take other precautions. In some cases, you may have to stop taking one of the medicines. This applies especially to the medicines listed below taken at the same time as Telmizan:

• Lithium-containing medicines to treat some types of depression.

• Medicines that may increase blood potassium levels such as salt substitutes containing potassium, potassium-sparing diuretics (certain 'water tablets'), ACE inhibitors, angiotensin II receptor blockers, NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.

• Diuretics ('water tablets'), especially if taken in high doses together with Telmizan, may lead to excessive loss of body water and low blood pressure (hypotension).

• If you are taking an ACE-inhibitor or aliskiren (see also information under the headings "Do not take Telmizan" and "Warnings and precautions").

• Digoxin.

The effect of Telmizan may be reduced when you take NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen) or corticosteroids.

Telmizan may increase the blood pressure lowering effect of other medicines used to treat high blood pressure or of medicines with blood pressure lowering potential (e.g. baclofen, amifostine). Furthermore, low blood pressure may be aggravated by alcohol, barbiturates, narcotics, or antidepressants. You may notice this as dizziness when standing up. You should consult with your doctor if you need to adjust the dose of your other medicine while taking Telmizan.

Pregnancy and breast-feeding

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Telmizan before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Telmizan. Telmizan is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Telmizan is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is a newborn or was born prematurely.

Driving and using machines

Some people may experience side effects such as fainting or a feeling of spinning (vertigo) when taking Telmizan. If you experience these side effects, do not drive or operate machinery.

Telmizan contains starch

This medicine contains 20 mg of starch in each tablet.

4. How to take Telmizan

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is one tablet a day. Try to take the tablet at the same time each day. You can take Telmizan with or without food. The tablets should be swallowed whole with some water or other non-alcoholic drink. It is important that you take Telmizan every day until your doctor tells you otherwise. If you have the impression that the effect of Telmizan is too strong or too weak, talk to your doctor or pharmacist. For the treatment of high blood pressure, the usual dose of Telmizan for most patients is one 40 mg tablet once a day to control blood pressure over the 24-hour period. Telmizan may be used in combination with diuretics ('water tablets') such as hydrochlorothiazide, which has been shown to have an additive

blood pressure lowering effect with Telmizan. For the reduction of cardiovascular events, the usual dose of Telmizan is one 40 mg tablet once a day. At the beginning of the preventive therapy with Telmizan 40 mg, blood pressure should be frequently monitored. If your liver is not working properly, the usual dose should not exceed 40 mg once daily.

If you take more Telmizan than you should

If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately.

If you forget to take Telmizan

If you forget to take a dose, do not worry. Take it as soon as you remember, then carry on as before. If you do not take your tablet on one day, take your normal dose on the next day. Do not take a double dose to make up for forgotten individual doses. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

5. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some side effects can be serious and need immediate medical attention.
You should see your doctor immediately if you experience any of the following symptoms: Sepsis* (often called "blood poisoning," is a severe infection with a whole-body inflammatory response), rapid swelling of the skin and mucosa (angioedema); these side effects are rare (may affect up to 1 in 1,000 people) but are extremely serious, and patients should stop taking the medicine and see their doctor immediately. If these effects are not treated, they could be fatal.

Common side effects (may affect up to 1 in 10 people): Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.

Uncommon side effects (may affect up to 1 in 100 people): Urinary tract infections, upper respiratory tract infections (e.g., sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anemia), high potassium levels, difficulty falling asleep, feeling sad (depression), fainting (syncope), feeling of spinning (vertigo), slow heart rate (bradycardia), low blood pressure (hypotension) in users treated for high blood pressure, dizziness on standing up (orthostatic hypotension), shortness of breath, cough, abdominal pain, diarrhea, pain in the belly, bloating, vomiting, itching, increased sweating, drug rash, back pain, muscle cramps, muscle pain (myalgia), kidney impairment (including acute kidney failure), pain in the chest, feeling of weakness, and increased level of creatinine in the blood.

Rare side effects (may affect up to 1 in 1,000 people): Sepsis* (often called "blood poisoning," is a severe infection with a whole-body inflammatory response which can lead to death), increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), severe allergic reaction (anaphylactic reaction), allergic reaction (e.g., rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), feeling anxious, somnolence, impaired vision, fast heartbeat (tachycardia), dry mouth, discomfort in the belly, taste disturbance (dysgeusia), abnormal liver function (Japanese patients are more likely to experience this side effect), rapid swelling of the skin and mucosa which can also lead to death (angioedema including fatal outcome), eczema (a skin disorder), redness of skin, hives (urticaria), severe drug rash, joint pain (arthralgia), pain in extremity, tendon pain, flu-like illness, decreased haemoglobin (a blood protein), increased levels of uric acid, increased hepatic enzymes or creatine phosphokinase in the blood, low levels of sodium.

Very rare side effects (may affect up to 1 in 10,000 people): Progressive scarring of lung tissue (interstitial lung disease)**.

Not known

Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting, and diarrhea has been reported after the use of similar products.

*The event may have happened by chance or could be related to a mechanism currently not known.
** Cases of progressive scarring of lung tissue have been reported during intake of Telmizan. However, it is not known whether Telmizan was the cause.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly through the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), the Spanish Agency for Medicines and Health Products. Visit the AEMPS website and fill out the report form at https://www.aemps.gob.es. By reporting side effects, you can help provide more information on the safety of this medicine.

6. How to store Telmizan

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP." The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from moisture. Remove your Telmizan tablet from the blister only directly prior to intake.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

7. Contents of the pack and other information

What Telmizan contains

The active substance is telmisartan. Each tablet contains 40 mg telmisartan. The other ingredients are starch, microcrystalline cellulose (MCC), talc, and magnesium stearate.

What Telmizan looks like and contents of the pack

Telmizan 40 mg tablets are white, oblong-shaped.

Telmizan is available in blister packs containing 28 tablets, in unit dose blister packs containing 28 tablets.

Manufacturer
Tayer Pharma Spain,
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Annex 2

Prospecto: Información para el usuario
Telmizan 40 mg comprimidos
Telmisartán

Lea todo este prospecto detenidamente antes de empezar a tomar este medicamento, ya que contiene información importante.

Conserve este prospecto. Puede que tenga que volver a leerlo. Si tiene alguna duda, consulte a su médico o farmacéutico. Este medicamento se le ha recetado solo a usted. No se lo dé a otras personas. Podría perjudicarles, incluso si sus síntomas son los mismos que los suyos. Si experimenta algún efecto secundario, consulte a su médico o farmacéutico, incluso si se trata de posibles efectos secundarios que no aparecen en este prospecto. Consulte la sección 4.

¿Qué contiene este prospecto?

1. Qué es Telmizan y para qué se utiliza

Telmizan pertenece a una clase de medicamentos conocidos como bloqueadores de los receptores de angiotensina II. La angiotensina II es una sustancia producida en el cuerpo que provoca el estrechamiento de los vasos sanguíneos, aumentando así la presión arterial. Telmizan bloquea el efecto de la angiotensina II, relajando los vasos sanguíneos y reduciendo la presión arterial. Telmizan se utiliza para tratar la hipertensión esencial (presión arterial alta) en adultos. «Esencial» significa que la presión arterial alta no está causada por ninguna otra afección. La presión arterial alta, si no se trata, puede dañar los vasos sanguíneos de varios órganos, lo que en ocasiones puede provocar un infarto de miocardio, insuficiencia cardíaca o renal, un accidente cerebrovascular o ceguera. Generalmente, la presión arterial alta no presenta síntomas antes de que se produzca el daño. Por lo tanto, es importante medirse la presión arterial regularmente para verificar que se encuentre dentro del rango normal. Telmizan también se utiliza para reducir los eventos cardiovasculares (es decir, infarto de miocardio o accidente cerebrovascular) en adultos con riesgo de sufrir un infarto de miocardio o un accidente cerebrovascular, ya sea por un suministro de sangre reducido o bloqueado al corazón o las piernas, por haber sufrido un accidente cerebrovascular o por tener diabetes de alto riesgo. Su médico puede indicarle si tiene un alto riesgo de sufrir estos eventos.

2. Qué necesita saber antes de tomar Telmizan

No tome Telmizan si:

• es alérgico al telmisartán o a cualquiera de los demás componentes de este medicamento (incluidos en la sección 6).

• está embarazada de más de 3 meses. (También es recomendable evitar Telmizan al principio del embarazo; consulte la sección sobre embarazo).

• tiene problemas hepáticos graves, como colestasis u obstrucción biliar (problemas con el drenaje de la bilis del hígado y la vesícula biliar), o cualquier otra enfermedad hepática grave.

• tiene diabetes o insuficiencia renal y está en tratamiento con un medicamento para bajar la presión arterial que contiene aliskiren. Si se encuentra en alguna de las situaciones anteriores, informe a su médico o farmacéutico antes de tomar Telmizan.

3. Advertencias y precauciones

Consulte a su médico antes de tomar Telmizan si padece o ha padecido alguna de las siguientes afecciones o enfermedades:

• Enfermedad renal o trasplante de riñón.

• Estenosis de la arteria renal (estrechamiento de los vasos sanguíneos de uno o ambos riñones).
• Enfermedad hepática.

• Problemas cardíacos.

• Niveles elevados de aldosterona (retención de agua y sal en el cuerpo junto con desequilibrio de varios minerales en la sangre).

• Presión arterial baja (hipotensión), que es probable que ocurra si está deshidratado (pérdida excesiva de agua corporal) o tiene deficiencia de sal debido, por ejemplo, a terapia con diuréticos ('comprimidos de agua'), dieta baja en sal, diarrea o vómitos.

• Niveles elevados de potasio en la sangre.

• Diabetes.

Hable con su médico antes de tomar Telmizan:

- si está tomando alguno de los siguientes medicamentos utilizados para tratar la presión arterial alta:
- un inhibidor de la ECA (por ejemplo, enalapril, lisinopril, ramipril), en particular, si tiene problemas renales relacionados con la diabetes.
- Aliskiren.
  Su médico podría controlar su función renal, presión arterial y niveles de electrolitos (p. ej., potasio) en sangre periódicamente. Consulte también la información en el apartado «No tome Telmizan».
- si está tomando digoxina.

Consulte a su médico si experimenta dolor abdominal, náuseas, vómitos o diarrea después de tomar Telmizan. Su médico decidirá el tratamiento adicional. No deje de tomar Telmizan por su cuenta.
Debe informar a su médico si cree que está (o podría estar) embarazada. No se recomienda tomar Telmizan al inicio del embarazo y no debe tomarse si tiene más de 3 meses de embarazo, ya que puede causar daños graves a su bebé si se usa en esa etapa (consulte la sección sobre embarazo).
En caso de cirugía o anestesia, debe informar a su médico que está tomando Telmizan. Telmizan puede ser menos eficaz para reducir la presión arterial en pacientes de raza negra.

Niños y adolescentes

No se recomienda el uso de Telmizan en niños y adolescentes hasta la edad de 18 años.

Uso de otros medicamentos y Telmizan.

Informe a su médico o farmacéutico si está tomando, ha tomado recientemente o podría tener que tomar cualquier otro medicamento. Es posible que su médico deba ajustar la dosis de estos otros medicamentos o tomar otras precauciones. En algunos casos, es posible que deba dejar de tomar alguno de los medicamentos. Esto se aplica especialmente a los medicamentos enumerados a continuación que se toman al mismo tiempo que Telmizan:

• Medicamentos que contienen litio para tratar algunos tipos de depresión.

• Medicamentos que pueden aumentar los niveles de potasio en sangre, como sustitutos de la sal que contienen potasio, diuréticos ahorradores de potasio (ciertos "comprimidos para orinar"), inhibidores de la ECA, antagonistas de los receptores de angiotensina II, AINE (medicamentos antiinflamatorios no esteroideos, p. ej., aspirina o ibuprofeno), heparina, inmunosupresores (p. ej., ciclosporina o tacrolimus) y el antibiótico trimetoprima.

• Los diuréticos ("comprimidos para orinar"), especialmente si se toman en dosis altas junto con Telmizan, pueden provocar una pérdida excesiva de agua corporal y presión arterial baja (hipotensión).

• Si está tomando un inhibidor de la ECA o aliskiren (consulte también la información bajo los encabezados "No tome Telmizan" y "Advertencias y precauciones").

• Digoxina. El efecto de Telmizan puede reducirse cuando toma AINE. (antiinflamatorios no esteroideos, p. ej., aspirina o ibuprofeno) o corticosteroides. Telmizan puede aumentar el efecto hipotensor de otros medicamentos utilizados para tratar la hipertensión o de medicamentos con potencial hipotensor (p. ej., baclofeno, amifostina). Además, la presión arterial baja puede verse agravada por el alcohol, los barbitúricos, los narcóticos o los antidepresivos. Puede notar mareos al ponerse de pie. Consulte a su médico si necesita ajustar la dosis de otros medicamentos mientras toma Telmizan.

Embarazo y lactancia

Debe informar a su médico si cree que está (o podría estar) embarazada. Su médico generalmente le recomendará que deje de tomar Telmizan antes de quedarse embarazada o tan pronto como sepa que está embarazada, y le recomendará que tome otro medicamento en lugar de Telmizan. No se recomienda tomar Telmizan al inicio del embarazo y no debe tomarse a partir del tercer mes de embarazo, ya que puede causar daños graves a su bebé si se usa después del tercer mes.

Lactancia materna

Informe a su médico si está amamantando o está a punto de comenzar. No se recomienda el uso de Telmizan en madres en período de lactancia, y su médico podría indicarle otro tratamiento si desea amamantar, especialmente si su bebé es recién nacido o prematuro.

Conducción y uso de máquinas

Algunas personas pueden experimentar efectos secundarios como desmayos o vértigo al tomar Telmizan. Si experimenta estos efectos secundarios, no conduzca ni maneje maquinaria.

Telmizan contiene almidón

Este medicamento contiene 20 mg de almidón en cada comprimido.

4. Cómo tomar Telmizan

Siga exactamente las instrucciones de administración de este medicamento indicadas por su médico. En caso de duda, consulte a su médico o farmacéutico. La dosis recomendada es de un comprimido al día. Intente tomar el comprimido a la misma hora cada día. Puede tomar Telmizan con o sin alimentos. Los comprimidos deben tragarse enteros con un poco de agua u otra bebida

no alcohólica. Es importante que tome Telmizan todos los días hasta que su médico le indique lo contrario. Si considera que el efecto de Telmizan es demasiado fuerte o demasiado débil, consulte a su médico o farmacéutico. Para el tratamiento de la hipertensión arterial, la dosis habitual de Telmizan para la mayoría de los pacientes es de un comprimido de 40 mg una vez al día para controlar la presión arterial durante un período de 24 horas. Telmizan puede utilizarse en combinación con diuréticos («comprimidos para orinar») como la hidroclorotiazida, que ha demostrado tener un efecto aditivo en la reducción de la presión arterial con Telmizan. Para reducir los eventos cardiovasculares, la dosis habitual de Telmizan es un comprimido de 40 mg una vez al día. Al inicio del tratamiento preventivo con Telmizan 40 mg, se debe controlar la presión arterial con frecuencia. Si su hígado no funciona correctamente, la dosis habitual no debe superar los 40 mg una vez al día.

Si toma más Telmizan del que debe

Si accidentalmente toma demasiados comprimidos, póngase en contacto inmediatamente con su médico, farmacéutico o con el servicio de urgencias del hospital más cercano.

Si olvida tomar Telmizan:

Si olvida tomar una dosis, no se preocupe. Tómela en cuanto se acuerde y continúe como antes. Si no toma su comprimido un día, tome su dosis habitual al día siguiente. No tome una dosis doble para compensar las dosis olvidadas. Si tiene alguna otra duda sobre el uso de este medicamento, consulte a su médico o farmacéutico.

5. Posibles efectos secundarios

Como todos los medicamentos, este medicamento puede causar efectos secundarios, aunque no todas las personas los sufran. Algunos efectos secundarios pueden ser graves y requieren atención médica inmediata. Consulte a su médico de inmediato si experimenta alguno de los siguientes síntomas: sepsis* (a menudo llamada "infección de la sangre" o "infección de la sangre" o "infección grave" con una respuesta inflamatoria generalizada), inflamación rápida de la piel y las mucosas (angioedema); estos efectos secundarios son poco frecuentes (pueden afectar hasta a 1 de cada 1000 personas), pero son extremadamente graves, por lo que los pacientes deben suspender el medicamento y consultar a su médico de inmediato. Si no se tratan, estos efectos podrían ser mortales.

Efectos secundarios comunes (pueden afectar hasta 1 de cada 10 personas): Presión arterial baja (hipotensión) en usuarios tratados para la reducción de eventos cardiovasculares.
Efectos secundarios poco frecuentes (pueden afectar hasta 1 de cada 100 personas): Infecciones del tracto urinario, infecciones del tracto respiratorio superior (p. ej., dolor de garganta, senos paranasales inflamados, resfriado común), deficiencia de glóbulos rojos (anemia), niveles altos de potasio, dificultad para conciliar el sueño, sensación de tristeza (depresión), desmayos (síncope), sensación de dar vueltas (vértigo), ritmo cardíaco lento (bradicardia), presión arterial baja (hipotensión) en usuarios tratados por presión arterial alta, mareos al ponerse de pie (hipotensión ortostática), dificultad para respirar, tos, dolor abdominal, diarrea, dolor en el vientre, hinchazón, vómitos, picazón, aumento de la sudoración, sarpullido por medicamentos, dolor de espalda, calambres musculares, dolor muscular (mialgia), insuficiencia renal (incluida insuficiencia renal aguda), dolor en el pecho, sensación de debilidad y aumento del nivel de creatinina en la sangre.
Efectos secundarios raros (pueden afectar hasta 1 de cada 1000 personas): Sepsis* (a menudo llamada "envenenamiento de la sangre", es una infección grave con una respuesta inflamatoria de todo el cuerpo que puede causar la muerte), aumento de ciertos glóbulos blancos (eosinofilia), bajo recuento de plaquetas (trombocitopenia), reacción alérgica grave (reacción anafiláctica), reacción alérgica (p. ej., sarpullido, picazón, dificultad para respirar, sibilancias, hinchazón de la cara o presión arterial baja), niveles bajos de azúcar en sangre (en pacientes diabéticos), sensación de ansiedad, somnolencia, problemas de visión, ritmo cardíaco acelerado

(taquicardia), boca seca, malestar abdominal, alteración del gusto (disgeusia), función hepática anormal (los pacientes japoneses son más propensos a experimentar este efecto secundario), hinchazón rápida de la piel y las mucosas que también puede causar la muerte (angioedema, incluido un desenlace mortal), eccema (un trastorno de la piel), enrojecimiento de la piel, ronchas (urticaria), sarpullido medicamentoso grave, dolor en las articulaciones (artralgia), dolor en las extremidades, dolor en los tendones, enfermedad parecida a la gripe, disminución de la hemoglobina (una proteína de la sangre), aumento de los niveles de ácido úrico, aumento de las enzimas hepáticas o de la creatina fosfoquinasa en la sangre, niveles bajos de sodio.
Efectos secundarios muy raros (pueden afectar hasta 1 de cada 10.000 personas): Cicatrización progresiva del tejido pulmonar (enfermedad pulmonar intersticial)**. Frecuencia

no conocida: Angioedema intestinal: se ha reportado una inflamación intestinal que se presenta con síntomas como dolor abdominal, náuseas, vómitos y diarrea tras el uso de productos similares.

*El evento pudo haber ocurrido por casualidad o estar relacionado con un mecanismo actualmente desconocido.
**Se han reportado casos de cicatrización progresiva del tejido pulmonar durante la administración de Telmizan. Sin embargo, se desconoce si Telmizan fue la causa.

Notificación de efectos adversos:

Si experimenta cualquier efecto adverso, consulte a su médico o farmacéutico, incluso si se trata de posibles efectos adversos que no aparecen en este prospecto. También puede notificar los efectos adversos directamente a través de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Visite la página web de la AEMPS y rellene el formulario de notificación en https://www.aemps.gob.es . Al notificar los efectos adversos, puede contribuir a proporcionar más información sobre la seguridad de este medicamento.

6. Cómo conservar Telmizan:

Mantenga este medicamento fuera de la vista y del alcance de los niños. No lo utilice después de la fecha de caducidad que aparece en el envase después de "CAD". La fecha de caducidad es el último día del mes correspondiente. Este medicamento no requiere condiciones especiales de temperatura de conservación. Consérvelo en el envase original para protegerlo de la humedad. Extraiga el comprimido de Telmizan del blíster justo antes de tomarlo. No tire ningún medicamento por el desagüe ni a la basura doméstica. Pregunte a su farmacéutico cómo desechar los medicamentos que ya no utiliza. Estas medidas ayudarán a proteger el medio ambiente.

7. Contenido del envase y otra información

Composición de Telmizan:

El principio activo es telmisartán. Cada comprimido contiene 40 mg de telmisartán. Los demás componentes son almidón, celulosa microcristalina (CCM), talco y estearato de magnesio.

Aspecto del producto y contenido del envase

Los comprimidos de Telmizan 40 mg son de color blanco y tienen forma oblonga. Telmizan se presenta en blísteres de 28 comprimidos y en blísteres de dosis unitaria de 28 comprimidos.

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