Public Assessment Report

Decentralised Procedure

Telmark 20, 40 and 80mg Film-coated Tablets

(Telmisartan)

UK/H/2634/01-03/DC

UK licence no: PL 33882/0036-8

Applicant: Glenmark Pharmaceuticals SRO
LAY SUMMARY

On 23rd March 2011, the Concerned Member States (CMSs) and the Reference Member State (RMS) agreed to grant Marketing Authorisations to Glenmark Pharmaceuticals s.r.o for the medicinal products Telmark 20, 40 and 80mg Film-coated Tablets. The marketing authorisations were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 19th April 2011.

These medicines are only available on prescription from your doctor.

Telmark belong to a class of medicines known as angiotensin II receptor antagonists. Angiotensin II is a substance produced in your body which causes your blood vessels to narrow, thus increasing your blood pressure. Telmark block the effect of angiotensin II so that the blood vessels relax, and your blood pressure is lowered.

Telmark is used to treat essential hypertension (high blood pressure). If this is not treated, it 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. This product is also used to reduce cardiovascular events (i.e. heart attack or stroke) in patients who are at risk because they have a reduced or blocked blood supply to the heart or legs, or have had a stroke or have high risk diabetes.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Telmark 20, 40 and 80mg Film-coated Tablets outweigh the risks. Hence, Marketing Authorisations have been granted.
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Module 6  Steps taken after initial procedure
# Module 1

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<td>Glenmark Pharmaceuticals s.r.o, Hvezdova 1716/2b, 140 78 Praha 4, Czech Republic</td>
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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Telmark 20mg film-coated tablets
Telmark 40mg film-coated tablets
Telmark 80mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20mg Telmark.
Excipients: 108.675mg lactose (as lactose monohydrate)

Each tablet contains 40mg Telmark.
Excipients: 217.35mg lactose (as lactose monohydrate)

Each tablet contains 80mg Telmark.
Excipients: 434.70mg lactose (as lactose monohydrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Yellow coloured circular shaped film coated tablets with ‘20’ engraved on one side and ‘T’ engraved on other side

Yellow coloured capsule shaped film coated tablets with ‘40’ engraved on one side and ‘T’ engraved on other side.

Yellow coloured capsule shaped film coated tablets with ‘80’ engraved on one side and ‘T’ engraved on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension
Treatment of essential hypertension in adults.

Cardiovascular prevention
Reduction of cardiovascular morbidity in patients with:
  i) manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or
  ii) type 2 diabetes mellitus with documented target organ damage

4.2 Posology and method of administration
Treatment of essential hypertension:
The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of Telmark can be increased to a maximum of 80 mg once daily. Alternatively, Telmark may be used in combination with thiazide-type diuretics such as hydrochlorothiazide, which has been shown to have an additive blood pressure lowering effect with Telmark. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment (see section 5.1).

Cardiovascular prevention:
The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of Telmark are effective in reducing cardiovascular morbidity.
When initiating Telmark therapy for the reduction of cardiovascular morbidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.
Telmark may be taken with or without food.

Special patient population:
Renal impairment: No posology adjustment is required for patients with mild to moderate renal impairment. Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of 20 mg is recommended in these patients (see section 4.4).

Hepatic impairment: In patients with mild to moderate hepatic impairment, the posology should not exceed 40 mg once daily (see section 4.4).

Elderly
No dose adjustment is necessary for elderly patients.

Paediatric patients
Telmark Glenmark is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients (see section 6.1)

Second and third trimesters of pregnancy (see sections 4.4 and 4.6)

Biliary obstructive disorders

Severe hepatic impairment

4.4 Special warnings and precautions for use

Pregnancy:
Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hepatic impairment:
Telmark is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment (see section 4.3) since Telmark is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for Telmark. Telmark should be used only with caution in patients with mild to moderate hepatic impairment.

Renovascular hypertension:
There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation:
When Telmark is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmark in patients with recent kidney transplantation.

Intravascular hypovolaemia:
Symptomatic hypotension, especially after the first dose of Telmark, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, or vomiting. Such conditions should be corrected before the administration of Telmark. Volume and/or sodium depletion should be corrected prior to administration of Telmark.

Dual blockade of the renin-angiotensin-aldosterone system: As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Other conditions with stimulation of the renin-angiotensin-aldosterone system:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as Telmark has been associated with acute hypotension, hyperkalaemia, oliguria, or rarely acute renal failure (see section 4.8).
Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Telmark is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Hyperkalaemia:
The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.
In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.
Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated.
The main risk factors for hyperkalaemia to be considered are:
Diabetes mellitus, renal impairment, age (>70 years)
Combination with one or more other medicinal products that affect the renin-angiotensinaldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.
Intercurrent events, in particular dehydratation, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma).
Close monitoring of serum potassium in at risk patients is recommended (see section 4.5).

Lactose:
This product contains lactose monohydrate.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Ethnic differences:
As observed for angiotensin converting enzyme inhibitors, Telmark and the other angiotensin II receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Other:
As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.
As with other medicinal products acting on the renin-angiotensin-aldosterone system, Telmark may provoke hyperkalaemia (see section 4.4). The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).
The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements:
Angiotensin II receptor antagonists such as Telmark, attenuate diuretic induced potassium loss.
Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amilorida, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.
Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including Telmark. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products:
NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

In one study the co-administration of Telmark and ramipril led to an increase of up to 2.5 fold in the AUC0-24 and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Diuretics (thiazide or loop diuretics):
Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with Telmark.

To be taken into account with concomitant use

Other antihypertensive agents:
The blood pressure lowering effect of Telmark can be increased by concomitant use of other antihypertensive medicinal products. Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including Telmark: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route):
Reduction of the antihypertensive effect.

4.6 Pregnancy and lactation

Pregnancy:
The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4). Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation:
Because no information is available regarding the use of Telmark during breast-feeding, Telmark is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects
The overall incidence of adverse events reported with Telmark (41.4%) was usually comparable to placebo (43.9%) in placebo controlled trials in patients treated for hypertension. The incidence of adverse events was not dose related and showed no correlation with gender, age or race of the patients.

The safety profile of Telmark in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse drug reactions listed below have been accumulated from all clinical trials in patients treated with Telmark for hypertension and from post-marketing reports. The listing also takes into account serious adverse events and adverse events leading to discontinuation reported in three clinical long term studies including 21642 patients treated with Telmark for the reduction of cardiovascular morbidity for up to six years.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (\( \geq \frac{1}{10} \)); common (\( \geq \frac{1}{100} \) to <\( \frac{1}{10} \)); uncommon (\( \geq \frac{1}{1,000} \) to <\( \frac{1}{100} \)); rare (\( \geq \frac{1}{10,000} \) to <\( \frac{1}{1,000} \)); very rare (<\( \frac{1}{10,000} \)), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations
Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, Urinary tract infection including cystitis
Not known: Sepsis including fatal outcome

Blood and the lymphatic system disorders
Uncommon: Anaemia
Rare: Thrombocytopenia
Not known: Eosinophilia

Immune system disorders
Rare: Hypersensitivity
Not known: Anaphylactic reaction

Metabolism and nutrition disorders
Uncommon: Hyperkalaemia

Psychiatric disorders
Uncommon: Depression, insomnia
Rare: Anxiety

Nervous system disorders
Uncommon: Syncope

Eye disorders
Rare: Vision disturbance

Eye and labyrinth disorders
Uncommon: Vertigo

Cardiac disorders
Uncommon: Bradycardia
Rare: Tachycardia

Vascular disorders
Uncommon: Hypotension, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Gastrointestinal disorders
Uncommon: Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting
Rare: Stomach discomfort, dry mouth
Hepato-biliary disorders
Rare: Hepatic function abnormal/liver disorder

Skin and subcutaneous tissue disorders
Uncommon: Hyperhidrosis, pruritus, rash
Rare: Erythema, angioedema, drug eruption, toxic skin eruption, eczema
Not known: Urticaria

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia, back pain (e.g. sciatica), muscle spasm.
Rare: Arthralgia, pain in extremity
Not known: Tendon pain (tendinitis like symptoms)

Renal and urinary disorders
Uncommon: Renal impairment including acute renal failure

General disorders and administration site conditions
Uncommon: Chest pain, asthenia (weakness)
Rare: Influenza-like illness
Investigations
Uncommon: Blood creatinine increased
Rare: Blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased, haemoglobin decreased

1 In the PROFESS trial, an increased incidence of sepsis was observed with Telmark compared with placebo. The event may be a chance finding or related to a mechanism currently not known (see section 5.1).

2 Reported as common in patients with controlled blood pressure who were treated with Telmark for the reduction of cardiovascular morbidity on top of standard care.

4.9 Overdose
There is limited information available with regard to overdose in humans.
Symptoms: The most prominent manifestations of Telmark overdose were hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.
Treatment: Telmark is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC Code: C09CA07.
Mechanism of action:
Telmark is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmark displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmark does not exhibit any partial agonist activity at the AT1 receptor. Telmark selectively binds the AT1 receptor. The binding is long-lasting. Telmark does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by Telmark. Plasma aldosterone levels are decreased by Telmark. Telmark does not inhibit human plasma renin or block ion channels. Telmark does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin mediated adverse effects. In human, an 80 mg dose of Telmark almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.
Clinical efficacy and safety:
Treatment of essential hypertension
After the first dose of Telmark, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.
The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of Telmark in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure (SBP). In this respect data concerning diastolic blood pressure (DBP) are inconsistent.

In patients with hypertension Telmark reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of Telmark is comparable to that of agents representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing Telmark to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with Telmark, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension. The incidence of dry cough was significantly lower in patients treated with Telmark than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

**Cardiovascular prevention**

**ONTARGET (ONgoing Telmark Alone and in Combination with Ramipril Global Endpoint Trial)** compared the effects of Telmark, ramipril and the combination of Telmark and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.

Patients were randomized to one of the three following treatment groups: Telmark 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of Telmark 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.

Telmark showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the Telmark (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for Telmark vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among Telmark and ramipril treated patients, respectively.

Telmark was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08), p (non-inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

**TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to Telmark 80 mg (n = 2954) or placebo (n = 2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the Telmark and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of Telmark compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with Telmark than in patients treated with ramipril, whereas hypotension was more frequently reported with Telmark. Combining Telmark with ramipril did not add further benefit over ramipril or Telmark alone. CV mortality and all cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm.

Therefore the use of a combination of Telmark and ramipril is not recommended in this population. In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for Telmark compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking Telmark (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence
rate of sepsis associated with the use of Telmark may be either a chance finding or related to a mechanism not currently known.

5.2 Pharmacokinetic properties

Absorption:
Absorption of Telmark is rapid although the amount absorbed varies. The mean absolute bioavailability for Telmark is about 50%. When Telmark is taken with food, the reduction in the area under the plasma concentration-time curve \( \frac{AUC_{0-\infty}}{AUC_{0-\infty}} \) of Telmark varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether Telmark is taken fasting or with food.

Linearity/non-linearity:
The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. \( C_{\text{max}} \) and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution:
Telmark is largely bound to plasma protein (>99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (\( V_{dss} \)) is approximately 500 l.

Metabolism:
Telmark is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination:
Telmark is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration \( (C_{\text{max}}) \) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of Telmark taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy. After oral (and intravenous) administration, Telmark is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance \( (\text{Cl}_{\text{tot}}) \) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Special Populations

Gender effects:
Differences in plasma concentrations were observed, with \( C_{\text{max}} \) and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly patients:
The pharmacokinetics of Telmark do not differ between the elderly and those younger than 65 years.

Patients with renal impairment:
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmark is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Patients with hepatic impairment:
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%. The elimination half-life is not changed in patients with hepatic impairment.

5.3 Preclinical safety data

In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral saline supplementation.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.
There is no evidence of a teratogenic effect, but animal studies indicated some hazardous potential of Telmark to the postnatal development of the offspring such as lower body weight, delayed eye opening, and higher mortality. There was no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Hydroxide
Povidone (K-25)
Meglumine
Lactose Monohydrate
Crospovidone
Ferric oxide yellow (E172)
Magnesium Stearate

The film-coating contains:
Hypromellose
Titanium Dioxide (E171)
Macrogol-400
Talc
Ferric oxide yellow (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Aluminium/aluminium blisters – Cold formable aluminium foil and hard tempered aluminium foil
Pack sizes: Blister with 14, 15, 28, 30, 56, 60, 90 or 98 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Glenmark Pharmaceuticals s.r.o, Hvezdova 1716/2b, 140 78 Praha 4, Czech Republic

8 MARKETING AUTHORISATION NUMBER(S)
PL 33882/0036
PL 33882/0037
PL 33882/0038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/04/2011

10 DATE OF REVISION OF THE TEXT
19/04/2011
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

[Name to be completed nationally] 20mg film-coated tablet
[Name to be completed nationally] 40mg film-coated tablet
[Name to be completed nationally] 80mg film-coated tablet
telmisartan

Read all of this leaflet carefully before you start taking this medicine.

- 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. Do not pass it on to others. It may harm them, even if
their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet,
please tell your doctor or pharmacist.

In this leaflet:
1. What [Name to be completed nationally] is and what it is used for
2. Before you take [Name to be completed nationally]
3. How to take [Name to be completed nationally]
4. Possible side effects
5. How to store [Name to be completed nationally]
6. Further information

1. WHAT [Name to be completed nationally] IS AND WHAT IT IS USED FOR

[Name to be completed nationally] belongs to a class of medicines known as angiotensin II receptor
antagonists. Angiotensin II is a substance produced in your body which causes your blood vessels to
narrow, thus increasing your blood pressure. [Name to be completed nationally] blocks the effect of
angiotensin II so that the blood vessels relax, and your blood pressure is lowered.

[Name to be completed nationally] is used to treat essential hypertension (high blood pressure). ‘Essential’
means that the 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.

[Name to be completed nationally] is also used to reduce cardiovascular events (i.e. heart attack or stroke)
in patients who are at risk because they have a reduced or blocked blood supply to the heart or legs, or have
had a stroke or have high risk diabetes. Your doctor can tell you if you are at high risk for such events.

2. BEFORE YOU TAKE [Name to be completed nationally]

Do not take [Name to be completed nationally]
- If you are allergic (hypersensitive) to telmisartan or any of the other ingredients included in [Name to
be completed nationally] (see section Further information for a list of other ingredients).
- If you are more than 3 months pregnant. (It is also better to avoid [Name to be completed nationally]
in early pregnancy – see pregnancy section.)
- If you have severe liver problems such as cholestasis or biliary obstruction (problems with the drainage
of the bile from the liver and gall bladder) or any other severe liver disease.

If any of the above applies to you, tell your doctor or pharmacist before taking [Name to be completed
nationally]

**Take special care with [Name to be completed nationally]**

Please tell your doctor 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 diuretic therapy (water tablets), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.

You must tell your doctor if you think you are (or might become) pregnant. [Name to be completed nationally] 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 anaesthesia, you should tell your doctor that you are taking [Name to be completed nationally].

The use of [Name to be completed nationally] in children and adolescents up to the age of 18 years is not recommended.

As with all other angiotensin II receptor antagonists, [Name to be completed nationally] may be less effective in lowering the blood pressure in black patients.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Your doctor may need to change the dose of these other medicines 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 with [Name to be completed nationally].

- 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 antagonists, 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 [Name to be completed nationally], may lead to excessive loss of body water and low blood pressure (hypotension).

As with other blood pressure lowering medicines, the effect of [Name to be completed nationally] may be reduced when you take NSAIDs (non steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen) or corticosteroids.

[Name to be completed nationally] may increase the blood pressure lowering effect of other medicines used to treat high blood pressure.

**Taking [Name to be completed nationally] with food and drink**

You can take [Name to be completed nationally] with or without food.
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 [Name to be completed nationally] before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of [Name to be completed nationally]. [Name to be completed nationally] 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. [Name to be completed nationally] 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 newborn, or was born prematurely.

Driving and using machines
No information is available on the effect of [Name to be completed nationally] on the ability to drive or operate machinery. Some people feel dizzy or tired when they are treated for high blood pressure. If you feel dizzy or tired, do not drive or operate machinery.

Important information about some of the ingredients of [Name to be completed nationally]
[Name to be completed nationally] contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE [Name to be completed nationally]
Always take [Name to be completed nationally] exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose of [Name to be completed nationally] is one tablet a day. Try to take the tablet at the same time each day. You can take [Name to be completed nationally] with or without food. The tablets should be swallowed with some water or other non-alcoholic drink. It is important that you take [Name to be completed nationally] every day until your doctor tells you otherwise. If you have the impression that the effect of [Name to be completed nationally] is too strong or too weak, talk to your doctor or pharmacist.

For the treatment of high blood pressure, the usual dose of [Name to be completed nationally] for most patients is one 40 mg tablet once a day to control blood pressure over the 24-hour period. However sometimes your doctor may recommend a lower dose of 20 mg or a higher dose of 80 mg. [Name to be completed nationally] may also be used in combination with diuretics ("water tablets") such as hydrochlorothiazide which has been shown to have an additive blood pressure lowering effect with [Name to be completed nationally].

For reduction of cardiovascular events, the usual dose of [Name to be completed nationally] is one 80 mg tablet once a day. At the beginning of the preventive therapy with [Name to be completed nationally] 80 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 [Name to be completed nationally] 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 [Name to be completed nationally]
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 product, ask your doctor or pharmacist.

If you stop taking [Name to be completed nationally]

Do not stop taking [Name to be completed nationally] without talking to your doctor. Medicines for high blood pressure may need to be taken for the rest of your life. If you stop taking [Name to be completed nationally] your blood pressure will return to the level it was before treatment in a few days.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, [Name to be completed nationally] can cause side effects, although not everybody gets them.

These side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data

Common side effects may include:
Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.

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

Rare side effects may include:
Low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), feeling anxious, impaired vision, fast heart beat (tachycardia), upset stomach, dry mouth, abnormal liver function, severe drug rash, redness of skin, rapid swelling of the skin and mucosa (angioedema), eczema (a skin disorder), joint pain (arthritis), pain in extremity, flu-like illness, increased levels of uric acid, hepatic enzymes or creatine phosphokinase in the blood and decreased haemoglobin (a blood protein).

Side effects of unknown frequency may include:
Increase in certain white blood cells (eosinophilia), severe allergic reaction (anaphylactic reaction), hives (urticaria), tendon pain, sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory response which can lead to death).
In a long-term study involving more than 20,000 patients, more patients treated with telmisartan experienced sepsis compared with patients who received no telmisartan. The event may have happened by chance or could be related to a mechanism currently not known.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE** [Name to be completed nationally]

Keep out of the reach and sight of children.

Do not use [Name to be completed nationally] 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 storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

What [Name to be completed nationally] contains

- The active substance is telmisartan, each tablet contains 20mg/40mg/80mg telmisartan.
- The other ingredients are:

  Sodium Hydroxide  
  Povidone (K-25)  
  Meglumine  
  Lactose Monohydrate  
  Crospovidone  
  Ferric oxide yellow (E172)  
  Magnesium Stearate

The film-coating contains:

  Hydroxypropylmethylcellulose  
  Titanium Dioxide (E171)  
  Macrogol-400  
  Talc  
  Ferric oxide yellow (E172)

What [Name to be completed nationally] looks like and contents of the pack

[Name to be completed nationally] are yellow, circular shaped film coated tablets with ‘20’ engraved on one side and ‘T’ engraved on the other side.

[Name to be completed nationally] are yellow, capsule shaped film coated tablets with ‘40’ engraved on one side and ‘T’ engraved on the other side.

[Name to be completed nationally] are yellow, capsule shaped film coated tablets with ‘80’ engraved on one side and ‘T’ engraved on the other side.

[Name to be completed nationally] is available in blister packs containing 14, 15, 28, 30, 56, 60, 90 or 98 tablets.
Not all pack sizes may be marketed in your country.

**Marketing Authorisation Holder and Manufacturer**

To be completed nationally

This leaflet was last approved in [MM/YYYY].
Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton

1. NAME OF THE MEDICINAL PRODUCT

[Name to be completed nationally] 20mg film-coated tablets
[Name to be completed nationally] 40mg film-coated tablets
[Name to be completed nationally] 80mg film-coated tablets
telmisartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20mg telmisartan
Each film-coated tablet contains 40mg telmisartan
Each film-coated tablet contains 80mg telmisartan

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
14 tablets
15 tablets
28 tablets
30 tablets
56 tablets
60 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. EXPIRY DATE

EXP: mm/yyyy

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch: XXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE


[Name to be completed nationally] 20mg film-coated tablets
[Name to be completed nationally] 40mg film-coated tablets
[Name to be completed nationally] 80mg film-coated tablets

The braille conversion is:
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTER</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

[Name to be completed nationally] 20mg film-coated tablets
[Name to be completed nationally] 40mg film-coated tablets
[Name to be completed nationally] 80mg film-coated tablets
telmisartan

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

To be completed nationally

3. **EXPIRY DATE**

EXP: mm/yyyy

4. **BATCH NUMBER**

Batch: xxxxx

5. **OTHER**
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and the Concerned Member States (CMSs) consider that the applications for Telmark 20, 40 and 80mg Film-coated Tablets, in the treatment of essential hypertension in adults and reduction of cardiovascular morbidity in patients with manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage, could be approved.

These applications have been submitted under article 10(1) of Directive 2001/83/EC, as amended, as generic medicinal products to Micardis 20, 40 and 80 mg film-coated tablets, which were first granted to Boehringer Ingelheim Limited, through centralised procedures, EU/1/98/090/009-012, in 1998.

With the UK as the Reference Member State in these Decentralized Procedures (UK/H/2634/01-03/DC), Glenmark Pharmaceuticals s.r.o applied for the Marketing Authorisations for Telmark 20, 40 and 80mg Film-coated Tablets in Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovak Republic.

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II.

No new preclinical and clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. Bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All Member States agreed to grant respective licence for the above products at the end of procedure (Day 210 – 23rd March 2011). After a subsequent national phase, the UK granted a licence for these products on 19th April 2011 (PL 33882/0036-8).
## ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Telmark 20, 40 and 80mg Film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Telmisartan |
| Pharmacotherapeutic classification (ATC code) | C09CA07, Angiotensin II Antagonists, plain, |
| Pharmaceutical form and strength(s) | Film-coated Tablets, 20, 40 and 80mg |
| Reference numbers for the Decentralised Procedures | UK/H/2634/01-03/DC |
| Reference Member State | United Kingdom |
| Concerned Member States | Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovak Republic. |
| Marketing Authorisation Number(s) | PL 33882/0036-8 |
| Name and address of the authorisation holder | Glenmark Pharmaceuticals s.r.o Hvezdova 1716/2b, 140 78 Praha 4, Czech Republic |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Telmisartan


Structure:

![Structure of Telmisartan](image)

Molecular Formula: C₃₃H₃₀N₄O₂
Molecular Weight: 514.6
Appearance: White or slightly yellowish, crystalline powder. Practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride. It dissolves in 1M sodium hydroxide.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sodium hydroxide, povidone (K-25), meglumine, lactose monohydrate, crospovidone, ferric oxide yellow (E172), magnesium stearate making up the tablet core; and (Opadry 02B82506 Yellow) consisted of
hypromellose, titanium dioxide (E171), macrogol-400, talc and ferric oxide yellow (E172) comprising the film-coating.

All excipients comply with their respective European Pharmacopoeia monographs except Opadry 02B82506 Yellow, which comply with an in-house specification and ferric oxide yellow (E172) which complies with United States Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for all excipients.

It had been confirmed that the excipients used are free of TSE/BSE and the corresponding certificates issued by each supplier were suitably provided. This is acceptable.

**Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Micardis 20, 40 and 80mg tablets registered in the EU since 16th December 1988 via centralized procedure.

Comparative impurity and dissolution profiles have been presented for test and reference products.

**Manufacture**

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches have been provided. The results are satisfactory. The applicant has committed to perform process validation on future production full-scale batches.

**Finished Product Specification**

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**

The finished product is packed in Aluminium/aluminium blisters– Cold formable aluminium foil and hard tempered aluminium foil.

Pack sizes are 14, 15, 28, 30, 56, 60, 90 or 98 tablets

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years with no special storage condition has been set for these products. This is satisfactory.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labels are pharmaceutically acceptable.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Perindopril Tablets as the parent PIL. The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

The Marketing Authorisation Holder has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
The pharmacological, pharmacokinetic and toxicological properties of telmisartan are well-known.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of these products from a preclinical point of view.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted two bioequivalence studies with Telmisartan 20 mg (Study GRF-BS-010-08) and Telmisartan 80mg (Study GRF-BS-011-08) studies under fasting conditions comparing the test product with the reference products.

Study GRF-BS-010-08 (Telmisartan 20 mg)
An open label, single dose, randomized, two-period, two-treatment, two-sequence, crossover study performed to demonstrate the bioequivalence of Telmisartan 20mg tablets (test) and Micardis 20mg tablets (reference) in healthy male volunteers under fasting conditions.
A single dose of the investigational products (1 tablet of 20 mg or 80mg) was administered orally to each subject in each period with 240 ± 2 ml of water after an overnight fast. A washout period of 12 days was maintained between the two dosing days in each group.

Serial blood sampling before dosing and at 0.25, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 48.00 and 72.00 hours after drug administration was carried out in each group.

Results

**Study GRF-BS-010-08 (Telmisartan 20 mg)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Least Squares Means</th>
<th>Ratio</th>
<th>%CV</th>
<th>90% Confidence Interval</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>28</td>
<td>29.95</td>
<td>93.49</td>
<td>19.28</td>
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<tr>
<td>AUC (0-t) (ng.hr/mL)</td>
<td>398.61</td>
<td>402.95</td>
<td>98.92</td>
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<tr>
<td>AUC (0-∞) (ng.hr/mL)</td>
<td>438.72</td>
<td>445.54</td>
<td>98.47</td>
<td>13.92</td>
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**Study GRF-BS-011-08 (Telmisartan 80 mg)**

An open label, single dose, randomized, two-period, two-treatment, two-sequence, crossover study performed to demonstrate the bioequivalence of Telmisartan 80mg tablets (test) and Micardis 80mg tablets (reference) in healthy male volunteers under fasting conditions.

A single dose of the investigational products (1 tablet of 20 mg or 80mg) was administered orally to each subject in each period with 240 ± 2 ml of water after an overnight fast. A washout period of 12 days was maintained between the two dosing days in each group.

Serial blood sampling before dosing and at 0.25, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 48.00 and 72.00 hours after drug administration was carried out in each group.

Results

**Study GRF-BS-011-08 (Telmisartan 80 mg)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Least Squares Means</th>
<th>Ratio</th>
<th>%CV</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>338.95</td>
<td>370.09</td>
<td>91.58</td>
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<tr>
<td>AUC (0-t) (ng.hr/mL)</td>
<td>1666.31</td>
<td>1685.13</td>
<td>98.88</td>
<td>18.97</td>
</tr>
<tr>
<td>AUC (0-∞) (ng.hr/mL)</td>
<td>1841.80</td>
<td>1874.85</td>
<td>98.24</td>
<td>18.81</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for C<sub>max</sub> and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulations (Telmisartan 20mg and 80 mg Tablets) and the reference formulation (Micardis 20 mg and 80 mg Tablets). A biowaiver has been granted to the 40mg tablet based on the studies conducted in line with the requirements of the Committee for Proprietary Medicinal Products Notes for Guidance on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**).
Pharmacodynamics
No new data have been submitted and none are required for these generic applications.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

Expert Report
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms
The MAA forms are medically satisfactory.

Clinical Conclusion
There are no objections to the approval of these products from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Telmark 20, 40 and 80mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence have been demonstrated between the applicant’s Telmisartan 20mg and 80 mg Tablets and the reference product, Micardis 20 mg and 80 mg Tablets and the results can be extrapolated to the 40mg Film-coated Tablets.

No new or unexpected safety concerns arise from these applications.

The SmPC and PIL are satisfactory and consistent with those of the reference products. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with telmisartan is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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