HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use WIDAPLIK™ safely and effectively. See full prescribing information for WIDAPLIK.

WIDAPLIK (telmisartan, amlodipine and indapamide) tablets, for oral use
Initial U.S. Approval: 2025

WARNING: FETAL TOXICITY
See full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue WIDAPLIK as soon as possible (5.1, 8.1)**
- **Drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and death to the developing fetus (5.1, 8.1)**

----------INDICATIONS AND USAGE----------
WIDAPLIK is a combination tablet of telmisartan, an angiotensin II receptor blocker, amlodipine, a dihydropyridine calcium channel blocker and indapamide, a thiazide-like diuretic. Widaplik is indicated for the treatment of hypertension, including as initial treatment, to lower blood pressure. (1) Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

----------DOSAGE AND ADMINISTRATION----------
For initial treatment of hypertension, start with Widaplik (10 mg/ 1.25 mg/0.625 mg) or Widaplik (20 mg/2.5 mg/1.25 mg) orally once daily. Titrate up to a maximum dose of Widaplik (40 mg/5 mg/2.5 mg) orally once daily. (2.2) Dosage may be increased after 2 weeks to a maximum dose of 40 mg/5 mg/2.5 mg orally once daily to achieve more rapid control. (2.1)
Almost all of the antihypertensive effect is apparent within 2 weeks of initiating treatment. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: (telmisartan/amlodipine/indapamide) 10 mg/1.25 mg/ 0.625 mg, 20 mg/2.5 mg/1.25 mg, 40 mg/5 mg/2.5 mg (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, amlodipine, indapamide, or to other sulfonamide-derived drugs, or to any other component of this product (4)
- Do not co-administer aliskiren with Widaplik in patients with diabetes (4)
- Anuria (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypotension: Correct volume depletion prior to initiation (5.2)
- Electrolyte and Glucose Imbalances: Monitor serum electrolytes and glucose (5.3)
- Impaired Renal Function: Monitor renal function (5.4)
- Acute angle closure glaucoma can develop (5.5)
- Hyperuricemia may occur (5.6)

----------ADVERSE REACTIONS----------
The most common adverse reaction is symptomatic hypotension. Low sodium and potassium values were recorded more often with Widaplik compared to placebo (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact George Medicines Pty Limited at 1-888 508-2083 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- NSAIDs: Increased risk of renal impairment and loss of anti-hypertensive effect (7.1)
- If simvastatin is co-administered with Widaplik, do not exceed doses greater than 20 mg daily of simvastatin (7.2)
- Do not co-administer aliskiren with Widaplik in patients with diabetes (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Breastfeeding is not recommended (8.2)
- Geriatric Patients: Severe cases of hyponatremia, accompanied by hypokalemia have been reported with use of indapamide in elderly females; consider initiation at lower doses for patients ≥65 years of age (8.5)
- Hepatic Impairment: Monitor carefully and start treatment at low doses (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

6/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

.

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue Widaplik as soon as possible *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.
Drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and death to the developing fetus *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

1 INDICATIONS AND USAGE

Widaplik (telmisartan/amlodipine/indapamide) is indicated for the treatment of hypertension in adult patients, to lower blood pressure. Widaplik may be used as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including angiotensin II receptor blockers, dihydropyridine calcium channel blockers and thiazide-like diuretics. There are no controlled trials demonstrating risk reduction with Widaplik.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Patients with moderate or severe hypertension are at relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. Consider the patient's baseline blood pressure, the target goal, and the incremental likelihood of achieving the goal with a triple combination product compared with mono- or dual therapy when deciding whether to use Widaplik as initial therapy. Individual blood pressure goals may vary based upon the patient's risk.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Dose orally once daily. Dosage must be individualized and may be increased after 2 weeks of treatment. Almost all the antihypertensive effect is apparent within 2 weeks of initiating treatment. Swallow tablets whole. Do not cut, crush, or chew tablets. Widaplik may be taken with or without food.

Correct imbalances of intravascular volume- or salt-depletion, before initiating therapy with Widaplik *[see Warnings and Precautions (5.3)].*

2.2 Recommended Dosage

The recommended starting dosage is with Widaplik (10 mg/1.25 mg/0.625 mg) orally once daily or Widaplik (20 mg/2.5 mg/1.25 mg) orally once daily, based on anticipated need for blood pressure reduction.

In elderly patients consider starting with Widaplik (10 mg/1.25 mg/0.625 mg) orally once daily *[see Use in Specific Populations, Geriatric Use (8.5)].*

The maximum recommended dose is Widaplik (40 mg/5 mg/2.5 mg) orally once daily.

3 DOSAGE FORMS AND STRENGTHS

Widaplik tablets are available as follows:

- 10 mg/1.25 mg/0.625 mg: 10 mg telmisartan/1.25 mg amlodipine/0.625 mg indapamide tablets – white to off-white oval tablet, debossed with "ULD" on one side and plain on the other side.
- 20 mg/2.5 mg/1.25 mg: 20 mg telmisartan/2.5 mg amlodipine/1.25 mg indapamide tablets – white to off-white round tablet, debossed with "LD" on one side and plain on the other side.
- 40 mg/5 mg/2.5 mg: 40 mg telmisartan/5 mg amlodipine/2.5 mg indapamide tablets – white to off-white oval tablet, debossed with "SD" on one side and plain on the other side.

4 CONTRAINDICATIONS

Do not use in patients with anuria, known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, amlodipine, indapamide, or to other sulfonamide-derived drugs, or to any other component of this product.

Do not co-administer aliskiren with Widaplik in patients with diabetes *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Use of drugs that act on the renin-angiotensin-aldosterone system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Widaplik as soon as possible *[see Use in Specific Populations (8.1)].*

5.2 Hypotension

Widaplik can cause symptomatic hypotension. Patients with hypovolemia, salt depletion, or aortic stenosis are at increased risk. Monitor blood pressure and adjust dose as needed.
Hypotension leading to worsening angina and acute myocardial infarction can develop after starting or increasing the dose of Widaplik because of the amlodipine component, particularly in patients with severe obstructive coronary artery disease.

5.3 Electrolyte and Glucose Imbalances

Thiazide-like diuretics can cause hyponatremia, hypomagnesemia and hypokalemia and can also alter serum glucose and affect insulin requirements. Drugs that inhibit the renin angiotensin-aldosterone system can cause hyperkalemia. Patients with renal impairment or heart failure are at increased risk for hyperkalemia. Monitor serum electrolytes and glucose periodically.

5.4 Impaired Renal Function

Inhibiting the renin-angiotensin-aldosterone system or diuresis can precipitate renal dysfunction, oliguria and acute renal failure. Patients with severe congestive heart failure or renal dysfunction are at increased risk *[see Clinical Pharmacology (12.3)*]. Monitor renal function periodically and adjust dose as needed.

5.5 Acute Angle-Closure Glaucoma, Acute Myopia, and Choroidal Effusion

Sulfonamide or sulfonamide-derivative drugs, like indapamide, can cause an idiosyncratic reaction resulting in acute angle-closure glaucoma and elevated intraocular pressure with or without a noticeable acute myopic shift and/or choroidal effusions. Symptoms may include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated, the angle-closure glaucoma may result in permanent visual field loss. The primary treatment is to discontinue Widaplik as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

5.6 Hyperuricemia

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide-like diuretics.

6 ADVERSE REACTIONS

The following is discussed in more detail in other sections of the labeling:

- Fetal toxicity *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Electrolyte and Glucose Imbalances *[see Warnings and Precautions (5.3)]*
- Impaired Renal Function *[see Warnings and Precautions (5.4)]*
- Acute Angle-Closure Glaucoma, Acute Myopia, and Choroidal Effusion *[see Warnings and Precautions (5.5)]*
- Hyperuricemia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trial Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Widaplik
Safety data were obtained from two randomized controlled studies that included 1,680 randomized patients with hypertension of whom 782 received Widaplik. Given the well-established safety profiles of the component medicines, only serious adverse events and the following adverse events of special interest were recorded: symptomatic hypotension, abnormal laboratory findings (sodium, potassium, uric acid, glucose, lipids, creatinine, eGFR), headache, peripheral edema, or other reason for discontinuation of study medication.

Study 1
In Study 1 (NCT04518306), 295 adult patients who were not receiving antihypertensive treatment for two weeks with baseline home systolic blood pressure 130-154 mmHg were randomized in a 2:2:1 ratio to Widaplik (10 mg/1.25 mg/0.625 mg), Widaplik (20 mg/2.5 mg/1.25 mg), or placebo. The study was 4 weeks in duration and randomized 232 patients to Widaplik and 63 to placebo.

The proportion of patients who discontinued study medication due to an adverse event was 0% for Widaplik (10 mg/1.25 mg/0.625 mg), 5.1% for Widaplik (20 mg/2.5 mg/1.25 mg), and 1.6% for placebo. Symptomatic hypotension, hyponatremia, and hypokalemia were more common with Widaplik than placebo (see Table 1). Most cases were mild to moderate in severity.

Table 1: Adverse Reactions Reported in >2% of Patients Treated with Widaplik during the 4-Week Placebo-Controlled Treatment Period of Study 1

	Widaplik (10 mg/1.25 mg/ 0.625 mg) (n=113)	**Widaplik (20 mg/2.5 mg/ 1.25 mg)** (n=118)	**Placebo** (n=62)
Symptomatic hypotension n (%)	4 (3.5%)	6 (5.1%)	0 (0%)
Sodium <135 mmol/L at week 4, n (%)	4 (3.5%)	1 (0.8%)	0 (0%)
Potassium <3.5 mmol/L at week 4, n (%)	4 (3.5%)	6 (5.1%)	1 (1.6%)

Study 2
Study 2 (NCT04518293) enrolled 2,242 patients on 0-3 antihypertensive medications at the screening visit. After a 4-week active run-in period during which all patients were initially switched to Widaplik (20 mg/2.5 mg/1.25 mg), patients then entered a double-blind period where they were randomized 2:1:1:1 to either continue on Widaplik (20 mg/2.5 mg/1.25 mg) or switch to telmisartan/amlodipine (TA) 20 mg/2.5 mg, telmisartan/indapamide (TI) 20 mg/1.25 mg, or amlodipine/indapamide (AI) 2.5 mg/1.25 mg. After 6 weeks in the double-blind period, doses were doubled in all treatment groups and treatment was continued for an additional 6 weeks. The study randomized 551 patients to Widaplik and 834 to one of the two-drug combinations.

During the 4-week active run-in period on Widaplik, 3.2% of patients had symptomatic hypotension. During the run-in period, 3.2% of patients discontinued study medication due to an adverse event, including 0.8% of patients who discontinued due to symptomatic hypotension. Because of this run-in design, the proportion of patients with adverse reactions described below is lower than expected in practice (see Table 2). The proportion of patients who discontinued study medication due to an adverse event over the 12-week treatment period was 2.0% for Widaplik and 1.4%, 1.1%, and 1.4% for the telmisartan/indapamide, telmisartan/amlodipine, and amlodipine/indapamide groups, respectively. Most adverse reactions were generally mild to moderate in severity.

Table 2: Adverse Reactions Reported in >2% of Patients Treated with Widaplik during the 12-Week Treatment Period of Study 2

	Widaplik (n = 547)	**Telmisartan/ Indapamide** (n = 275)	**Telmisartan/ Amlodipine** (n = 282)	**Amlodipine/ Indapamide** (n = 276)
Symptomatic hypotension, n (%)	32 (5.9%)	11 (4.0%)	5 (1.8%)	4 (1.4%)
Sodium <135 mmol/L at week 12, n (%)	40 (7.3%)	19 (6.9%)	9 (3.2%)	10 (3.6%)
Potassium <3.5 mmol/L at week 12, n (%)	37 (6.8%)	13 (4.7%)	0 (0%)	35 (12.7%)

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing experience with telmisartan, amlodipine or indapamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Telmisartan
The most frequently reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioedema, urticaria, sweating increased, erythema, dyspepsia, diarrhea, pain, erectile dysfunction, abdominal pain, myalgia, eosinophilia, thrombocytopenia, anemia, and increased CPK, rhabdomyolysis, drug eruption (e.g., toxic skin eruption mostly reported as toxicoderma, rash, and urticaria).

Amlodipine
Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), extrapyramidal disorder.

Indapamide
Exacerbation of systemic lupus erythematous, choroidal effusion, acute myopia, and angle-closure glaucoma.

7 DRUG INTERACTIONS

7.1 Drug Interactions with Telmisartan

Aliskiren and other renin-angiotensin-aldosterone system (RAAS) inhibitors: Do not co-administer aliskiren with Widaplik in patients with diabetes. Most patients receiving the combination of two RAAS inhibitors do not obtain any additional benefit compared to monotherapy *[see Contraindications (4)]*. Avoid use of aliskiren with Widaplik in patients with renal impairment (GFR <60 mL/min) *[see Warnings and Precautions (5.4)].*

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Monitor digoxin levels when initiating, adjusting, and discontinuing Widaplik to keep the digoxin level within the therapeutic range.

Lithium: Increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Monitor serum lithium levels during concomitant use *[see Drug Interactions with Indapamide (7.3)]*.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving Widaplik and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

7.2 Drug Interactions with Amlodipine

Impact of other drugs on amlodipine
CYP3A Inhibitors
Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when Widaplik is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers
No information is available on the quantitative effects of CYP3A inducers on amlodipine.
Blood pressure should be closely monitored when Widaplik is co-administered with CYP3A inducers.

Sildenafil
Monitor for hypotension when sildenafil is co-administered with Widaplik.

Impact of amlodipine on other drugs
Simvastatin: Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on Widaplik to 20 mg daily.

Immunosuppressants: Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus and dose adjustment when appropriate is recommended.

7.3 Drug Interactions with Indapamide

Lithium: In general, diuretics should not be given concomitantly with lithium because they reduce its renal clearance and add a high risk of lithium toxicity. Read prescribing information for lithium preparations before use of such concomitant therapy.

Norepinephrine: Indapamide, like thiazide diuretics, may decrease arterial responsiveness to norepinephrine, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Widaplik can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin-aldosterone system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death (*see Clinical Considerations*). Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin-aldosterone system from other antihypertensive agents. Studies in rats and rabbits showed fetotoxicity only at maternally toxic doses of telmisartan (*see Data*). When pregnancy is detected, discontinue Widaplik as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major malformations and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions
Telmisartan
Use of drugs that act on the RAAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual

case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin-aldosterone system for a particular patient, apprise the mother of the potential risk to the fetus.

In patients taking Widaplik during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue Widaplik, unless it is considered lifesaving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe neonates with histories of *in utero* exposure to Widaplik for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Indapamide
Diuretics are known to cross the placental barrier and appear in cord blood. There may be hazards associated with this use such as fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in the adult.

Data

Animal Data
No reproductive toxicity studies have been conducted with Widaplik. However, these studies have been conducted for telmisartan, amlodipine and indapamide alone.

Telmisartan
No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m^2 basis, the MHRD of telmisartan (80 mg/day).

Amlodipine
No evidence of teratogenicity or embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the MRHD based on body surface area, respectively) during their respective periods of major organogenesis. However, for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

Indapamide
Reproduction studies have been performed in rats, mice and rabbits at doses up to 6,250 times the therapeutic human dose and have revealed no evidence of impaired fertility or harm to the fetus due to indapamide. Postnatal development in rats and mice was unaffected by pretreatment of parent animals during gestation.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Widaplik in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that amlodipine is present in human milk at an estimated median relative infant dose of 4.2%. No adverse effects of amlodipine on the breastfed infant have been observed. There is no available information on the effects of amlodipine on milk production. There is no information regarding the presence of telmisartan in human milk. Telmisartan is present in the milk of lactating rats *(see Data)*. It is not known whether indapamide is excreted in human milk. Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with Widaplik.

Data

Telmisartan was present in the milk of lactating rats at concentrations 1.5 to 2 times those found in plasma from 4 to 8 hours after administration.

8.4 Pediatric Use

Safety and effectiveness of Widaplik in pediatric patients have not been established.

Neonates with a history of *in utero* exposure to Widaplik

If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

8.5 Geriatric Use

Widaplik

In subgroup analysis in subjects ≥65 years (n= 176) the antihypertensive effect of Widaplik was not substantially different compared to younger subjects, however the number of elderly patients enrolled in both Widaplik studies was small.

Telmisartan

Of the total number of patients receiving telmisartan in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years and older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine

Clinical studies with amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Since elderly patients may have decreased clearance of amlodipine, start amlodipine at ≤2.5 mg *[see Dosage and Administration (2)].*

Indapamide
Clinical studies with indapamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Severe cases of hyponatremia, accompanied by hypokalemia have been reported with indapamide in elderly females *[see Warnings and Precautions (5.3)]*.

8.6 Hepatic Impairment

Because telmisartan, amlodipine and indapamide are hepatically cleared, initiate therapy at the lowest dose and titrate slowly *[see Clinical Pharmacology (12.3)].* The use of thiazide-like diuretics may precipitate hepatic coma because of fluid shifts.

10 OVERDOSAGE

Telmisartan
Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Amlodipine
Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the MRHD on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

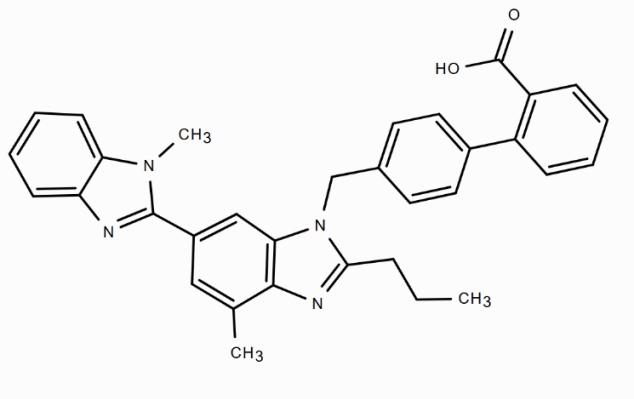
If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Indapamide
Symptoms of overdosage of indapamide include nausea, vomiting, weakness, gastrointestinal disorders and disturbances of electrolyte balance. In severe instances, hypotension and depressed respiration may be observed. If this occurs, support of respiration and cardiac circulation should be instituted. There is no specific antidote. An evacuation of the stomach is recommended by emesis and gastric lavage after which the electrolyte and fluid balance should be evaluated carefully.

11 DESCRIPTION

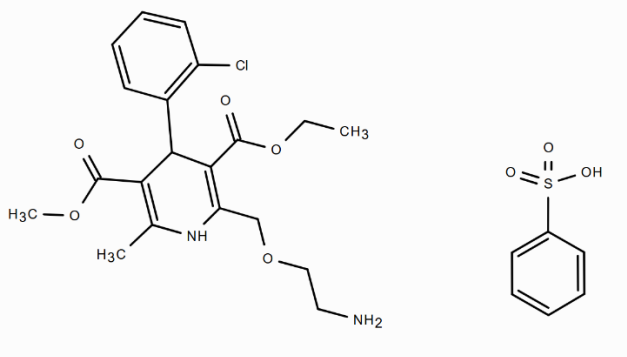
Widaplik is a fixed dose combination of telmisartan, amlodipine and indapamide.

Widaplik contains telmisartan, a non-peptide angiotensin II receptor (type AT1) antagonist. Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63, and the structural formula is:



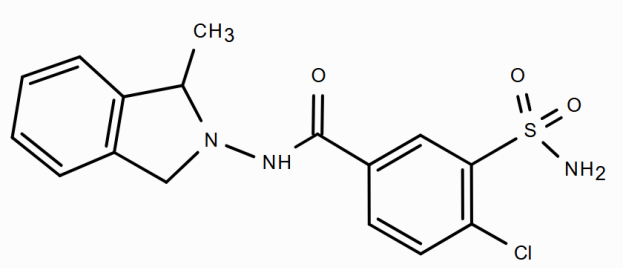
Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water, slightly soluble in methanol and soluble in strong base.

Widaplik contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker. Amlodipine besylate is chemically described as 3-ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$, its molecular weight is 567.1, and the structural formula is:



Amlodipine besylate is a white crystalline powder. It is slightly soluble in water and sparingly soluble in ethanol.

Widaplik contains indapamide, a thiazide-like diuretic. Indapamide is chemically described as 4-chloro-N-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide. Its empirical formula is $C_{16}H_{16}ClN_3O_3S$, its molecular weight is 365.84, and the structural formula is:



Indapamide is a white to off-white, crystalline powder. It is soluble in ethyl alcohol and practically insoluble in water.

Widaplik tablets are formulated in 3 strengths for oral administration

- 10 mg/1.25 mg/0.625 mg: combination of 10 mg telmisartan, with 1.25 mg amlodipine (equivalent to 1.73 mg amlodipine besylate), with 0.625 mg indapamide
- 20 mg/2.5 mg/1.25 mg: combination of 20 mg telmisartan, with 2.5 mg amlodipine (equivalent to 3.47 mg amlodipine besylate), with 1.25 mg indapamide
- 40 mg/5 mg/2.5 mg: combination of 40 mg telmisartan, with 5 mg amlodipine (equivalent to 6.94 mg amlodipine besylate), with 2.5 mg of indapamide

Widaplik also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, meglumine, microcrystalline cellulose, polyvinyl pyrrolidone, pregelatinized starch, and sodium hydroxide.

Widaplik tablets are hygroscopic and require protection from moisture. Widaplik tablets require protection from light.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active ingredients of Widaplik target 3 separate mechanisms involved in blood pressure regulation.

Telmisartan
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin-aldosterone system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT_1 receptor

than for the AT_2 receptor. The increased plasma levels of angiotensin following AT_1 receptor blockade with telmisartan may stimulate the unblocked AT_2 receptor.

Blockade of the renin-angiotensin-aldosterone system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Indapamide
Indapamide is a thiazide-like diuretic. Although the mechanism of action is not clear, indapamide appears to act principally on the distal convoluted tubules of the nephron. The drug enhances the excretion of sodium, chloride, and water by inhibiting the transport of sodium ions across the renal tubule. The hypovolemic action of indapamide is believed to be responsible for the drug's beneficial cardiovascular effects. Decreased plasma and extracellular fluid volume, along with a decreased peripheral vascular resistance (secondary to loss of sodium, or to vascular autoregulatory feedback systems), act to lower blood pressure in hypertensive patients who are receiving indapamide. The drug may also produce calcium-channel blockade in smooth muscle cells, thereby causing arteriolar vasodilation.

12.2 Pharmacodynamics

Widaplik is a combination of three drugs with antihypertensive properties: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, an angiotensin II receptor blocker, telmisartan and a thiazide-like diuretic, indapamide. All three components lower the blood pressure by reducing peripheral resistance, but through complementary mechanisms, each working at a separate site and blocking different effector pathways.

Widaplik has not been studied in indications other than hypertension.

Telmisartan
An oral dose of 80 mg telmisartan, a dose higher than in Widaplik, inhibited the pressor response of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Amlodipine
Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

With chronic once daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In clinical studies in which amlodipine was administered in combination with beta-blockers to

patients with either hypertension or angina, no adverse effects of electrocardiographic parameters were observed.

Pharmacodynamic Drug interactions

Sildenafil

When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect *[see Drug Interactions (7.2)].*

12.3 Pharmacokinetics

Absorption

Following single-dose oral administration of Widaplik (40 mg/5 mg/2.5 mg) to healthy subjects in the fasted state, the extent of absorption (AUC) and rate of absorption (C_{max}) of telmisartan was 750 ng.h/mL and 64.7 ng/mL, the AUC and C_{max} of amlodipine was 102,000 pg.h/mL and 2,850 pg/mL, and the AUC and C_{max} of indapamide was 2,170 ng.h/mL and 144 ng/mL, respectively. The peak plasma concentrations of amlodipine, telmisartan and indapamide are achieved at approximately 1.8 hours, 7.5 hours, and 0.9 hours, respectively, under fasting conditions.

Effect of Food

A food-effect study involving administration of Widaplik (40 mg/5 mg/2.5 mg) to healthy subjects after a high-fat, high calorie breakfast indicated that the C_{max} of telmisartan decreased 41%, while AUC remained unchanged, the C_{max} and AUC of amlodipine and indapamide remained unchanged, when compared to administration under fasting conditions. The T_{max} of telmisartan, amlodipine and indapamide was delayed by approximately 2 hours, 1 hour, and 1.5 hours, respectively, under fed conditions.

Distribution

Telmisartan

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 L indicating additional tissue binding.

Amlodipine

The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Indapamide

Indapamide is preferentially and reversibly taken up by the erythrocytes in the peripheral blood. The whole blood/plasma ratio is approximately 6:1 at the time of peak concentration and decreases to 3.5:1 at eight hours. From 71 to 79% of the indapamide in plasma is reversibly bound to plasma proteins.

Metabolism and Elimination

Telmisartan
Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Amlodipine
Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.
Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Indapamide
Indapamide is an extensively metabolized drug, with only about 7% of the total dose administered, recovered in the urine as unchanged drug during the first 48 hours after administration. The urinary elimination of ^{14}C-labeled indapamide and metabolites is biphasic with a terminal half-life of excretion of total radioactivity of 26 hours.

A minimum of 70% of a single oral dose is eliminated by the kidneys and an additional 23% by the gastrointestinal tract, probably including the biliary route. The half-life of indapamide in whole blood is approximately 14 hours.

Specific Populations

Geriatric Patients
Telmisartan: The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

Amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%.

Indapamide: The pharmacokinetics of indapamide in geriatric patients is unknown.

Male and Female Patients
Telmisartan: Plasma concentrations of telmisartan are generally 2 to 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.

Patients with Renal Impairment
Telmisartan: Renal impairment does not increase the AUC of telmisartan. Telmisartan is not removed from blood by hemodialysis.

Amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Indapamide: The effect of renal impairment on the pharmacokinetics of indapamide is unknown.

Patients with Hepatic Impairment
Telmisartan: In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% *[see Use in Specific Populations (8.6)]*.

Amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%.

Indapamide: The effect of hepatic impairment on the pharmacokinetics of indapamide is unknown *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Telmisartan
Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Amlodipine
In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Impact of other drugs on amlodipine
Co-administered cimetidine, magnesium- and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic

exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent *[see Drug Interactions (7.2)].*

Impact of amlodipine on other drugs
Amlodipine is a weak inhibitor of CYP3A and may increase exposure to CYP3A substrates.

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone *[see Drug Interactions (7.2)].*

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine *[see Drug Interactions (7.2)].*

Tacrolimus: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5- to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs *[see Drug Interactions (7.2)].*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Widaplik
No carcinogenicity, mutagenicity, or fertility studies have been conducted with this combination. However, these studies have been conducted for amlodipine, telmisartan and indapamide alone. Based on preclinical safety and human pharmacokinetic studies, there is no indication of any toxicologically significant adverse interaction between these components.

Telmisartan
There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1,000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the MRHD of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m^2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Amlodipine
Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5 mg, 1.25 mg, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m^2 basis, similar to the MRHD of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about 2.5 times the MRHD (calculations based on a 60 kg patient).

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m^2 basis).

Indapamide
Both mouse and rat lifetime carcinogenicity studies were conducted. There was no significant difference in the incidence of tumors between the indapamide-treated animals (up to 100 mg/kg/day) and the control groups.

Doses up to 6,250 times the therapeutic human dose have revealed no evidence of impaired fertility as tested in rats, mice and rabbits.

14 CLINICAL STUDIES

The efficacy of Widaplik in lowering blood pressure was evaluated in a randomized study designed to evaluate the efficacy and safety of two doses of Widaplik (10 mg/1.25 mg/0.625 mg and 20 mg/2.5 mg/1.25 mg) compared to placebo (Study 1, NCT04518306) and in a randomized study designed to evaluate the efficacy and safety of Widaplik (40 mg/5 mg/2.5 mg) as compared to each of its two-drug combinations at the same doses (Study 2, NCT04518293).

Study 1

Study 1 (NCT04518306) was a 4-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study that randomized 295 adults with systolic hypertension who were taking 0-1 antihypertensive medications at screening and who were at a low risk for cardiovascular disease per local guidelines (e.g., pooled cohorts equation 10-year atherosclerotic cardiovascular disease risk <10% in the United States). The study excluded patients with a clinic seated blood pressure ≥160/100 mmHg at screening and an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at randomization. Following a 2-week placebo run-in period during which any monotherapy was discontinued, eligible patients with a home systolic blood pressure between 130 and 154 mmHg were randomized 2:2:1 to receive Widaplik (10 mg/1.25 mg/0.625 mg), Widaplik (20 mg/2.5 mg/1.25 mg), or placebo. The primary endpoint was the change from randomization to Week 4 in home systolic blood pressure.

At baseline, mean age was 51 years (range 19 to 83 years), 44% of patients were male, 61% were White, 17% Black, and 21% Asian.

The change from randomization to Week 4 in home systolic and diastolic pressure in the Widaplik (10 mg/1.25 mg/0.625 mg), Widaplik (20 mg/2.5 mg/1.25 mg), and placebo arms, is shown in Table 3. Both doses of Widaplik showed statistically significant greater reductions in home systolic blood pressure compared to placebo (see Table 3). Most of the home systolic blood pressure lowering effect occurred within the first two weeks of treatment with Widaplik for both doses. The findings for clinic blood pressure were consistent with the results for home blood pressure.

Table 3: Changes from Randomization to Week 4 in Home Blood Pressure, Comparing Widaplik (10 mg/1.25 mg/0.625 mg) or Widaplik (20 mg/2.5 mg/1.25 mg) vs Placebo (Study 1)

	Placebo (N=63)	Widaplik 10 mg/1.25 mg/ 0.625 mg (N=113)	Widaplik 20 mg/2.5 mg/ 1.25 mg (N=119)
Home systolic blood pressure, mmHg			
Randomization, Mean (SD)	138.7 (6.9)	138.4 (6.7)	138.8 (6.3)
Week 4, Mean (SD)	136.4 (8.9)	129.2 (9.5)	128.0 (12.0)
LSM change from randomization, Mean (SE)	-2.2 (1.2)	-9.6 (1.0)	-10.4 (1.3)
Difference to placebo in LSM (95% CI) P-value	-	-7.3 (-10.2, -4.5) p <0.0001	-8.2 (-11.3, -5.2) p <0.0001
Home diastolic blood pressure, mmHg			
Randomization, Mean (SD)	85.8 (8.6)	85.2 (7.3)	86.9 (7.2)
LSM change from randomization, Mean (SE)	-1.1 (0.8)	-5.1 (0.8)	-6.6 (0.6)
Difference to placebo in LSM (95% CI)	-	-4.0 (-6.0, -2.0)	-5.5 (-7.3, -3.7)

CI= confidence interval; LSM = least squares mean; SD = standard deviation; SE = standard error.

Study 2

Study 2 (NCT04518293) was a 12-week, multi-center, randomized, double-blind, parallel group study designed to evaluate the efficacy of Widaplik up to 40 mg/5 mg/2.5 mg as compared to each of its two-drug combinations at the same doses: telmisartan/indapamide (TI), telmisartan/amlodipine (TA), or amlodipine/indapamide (AI).

Enrolled patients were required to have a mean systolic blood pressure of 140 to 179 mmHg if on no antihypertensive medications, 130 to 170 mmHg if on one, 120 to 160 mmHg if on two, or 110 to 150 mmHg if on three. The study excluded patients with a history of cardiovascular disease, New York Heart Association (NYHA) class III or IV congestive heart failure, or an eGFR <60 mL/min/ 1.73 m^2 at screening. Following discontinuation of any antihypertensive medications, 2,244 patients entered a 4-week, single-blind, run-in period where all patients received Widaplik (20 mg/2.5 mg/ 1.25 mg). After the 4-week run-in period, 1,385 patients with systolic blood pressure 110 to 154 mmHg were randomized 2:1:1:1 to Widaplik (20 mg/2.5 mg/1.25 mg); TA 20 mg/2.5 mg; TI 20 mg/1.25 mg; or AI 2.5 mg/1.25 mg. After Week 6 and through Week 12, doses in all 4 groups were doubled (Widaplik 40 mg/5 mg/2.5 mg, TA 40 mg/5 mg, TI 40 mg/2.5 mg, and AI 5 mg/2.5 mg). The primary endpoint was the change in home seated mean systolic blood pressure from randomization to Week 12.

At baseline, mean age was 59 years (range 20 to 91 years), 49% of patients were male, 46% were White, 5% were Black and 49% Asian.

The change from randomization to Week 12 in home systolic and diastolic blood pressure in the Widaplik (40 mg/5 mg/2.5 mg) arm and in each of the dual combination arms is shown in Table 4. Widaplik (40 mg/5 mg/2.5 mg) showed statistically significant greater reductions in home systolic

blood pressure compared to each of the dual combinations. The findings for clinic blood pressure were consistent with the results for home blood pressure.

Table 4: Changes from Randomization to Week 12 in Home Blood Pressure, Comparing Widaplik (40 mg/5 mg/2.5 mg) vs TA 40 mg/5 mg, TI 40 mg/2.5 mg, and AI 5 mg/2.5 mg (Study 2)

	Widaplik 40 mg/5 mg/ 2.5 mg (N=551)	Telmisartan/ Indapamide 40 mg/2.5 mg (N=276)	Telmisartan/ Amlodipine 40 mg/5 mg (N=282)	Amlodipine/ Indapamide 5 mg/2.5 mg (N=276)
Home systolic blood pressure, mmHg				
Randomization, Mean (SD)	128.7 (9.9)	128.9 (10.6)	128.4 (9.9)	129.2 (9.8)
Week 12, Mean (SD)	124.0 (10.4)	126.5 (11.6)	129.4 (11.1)	128.8 (10.8)
LSM change from randomization, Mean (SE)	-4.0 (0.5)	-1.5 (0.5)	1.4 (0.6)	0.5 (0.4)
Difference Widaplik vs dual comparator in LSM (95% CI) P-value	-	-2.5 (-3.7, -1.3) p <0.0001	-5.4 (-6.8, -4.1) p<0.0001	-4.4 (-5.8, -3.1) p<0.0001
Home diastolic blood pressure, mmHg				
Randomization, Mean (SD)	78.0 (9.0)	77.4 (8.5)	78.4 (9.3)	78.4 (8.6)
LSM change from randomization, Mean (SE)	-2.9 (0.3)	-0.8 (0.4)	0.5 (0.3)	0.7 (0.5)
Difference Widaplik vs dual comparator in LSM (95% CI)	-	-2.1 (-3.0, -1.2)	-3.4 (-4.1, -2.6)	-3.6 (-4.6, -2.6)

T=telmisartan, A=amlodipine, I=indapamide.
CI= confidence interval; LSM= least squares mean; SD= standard deviation; SE= standard error.

Widaplik's blood pressure lowering effect appeared consistent among subgroups defined by age, sex, and race.

There are no studies of Widaplik demonstrating reductions in cardiovascular risk in patients with hypertension; however, previous studies with amlodipine, indapamide and several angiotensin II receptor blockers, which are in the same pharmacological class as the telmisartan component, have demonstrated such benefits.

16 HOW SUPPLIED/STORAGE AND HANDLING

Widaplik 10 mg/1.25 mg/0.625 mg: White to off-white oval tablet, debossed with “ULD” on one side and plain on other side.

Widaplik 20 mg/2.5 mg/1.25 mg: White to off-white round tablet, debossed with “LD” on one side and plain on other side.

Widaplik 40 mg/5 mg/2.5 mg: White to off-white oval tablet, debossed with “SD” on one side and plain on other side.

Widaplik tablets are supplied in the following strengths and package configurations:

Tablet strength (telmisartan/amlodipine/indapamide)	**Package Configuration**	**NDC#**
10 mg/1.25 mg/0.625 mg	Bottles of 30 tablets	85502-001-30
20 mg/2.5 mg/1.25 mg	Bottles of 30 tablets	85502-002-30
40 mg/5 mg/2.5 mg	Bottles of 30 tablets	85502-003-30

Storage
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]*. Protect from moisture and light. Store and dispense the product in the original container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labelling (*see Patient Information*).

Pregnancy
Advise female patients of childbearing age about the consequences of exposure to Widaplik during pregnancy. Discuss treatment options with women planning to become pregnant. Tell patients to report pregnancies to their physicians as soon as possible *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Lactation
Advise nursing women not to breastfeed during treatment with Widaplik *[see Use in Specific Populations (8.2)]*.

Symptomatic Hypotension
Advise patients that lightheadedness can occur, especially during the first days of therapy, and to report it to their healthcare provider. Inform patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope. Advise patients to contact their healthcare provider if syncope occurs *[see Warnings and Precautions (5.2)]*.

Hyperuricemia
Advise patients to inform their healthcare provider if they experience signs or symptoms associated with hyperuricemia *[see Warnings and Precautions (5.6)]*.

Potassium Supplements

Advise patients not to use potassium supplements or salt substitutes that contain potassium without consulting the prescribing healthcare provider *[see Warnings and Precautions (5.3)].*

Widaplik™ is a registered trademark of George Medicines Pty Limited

Manufactured by:
Piramal Pharma Limited
Plot No. 67-70,
Sector II, Pithampur,
Dist. Dhar, Madhya
Pradesh 454775, India