

# DATA SHEET

## NAME OF MEDICINE

TAZKO®  
felodipine - ramipril tablets 2.5/2.5 mg  
felodipine - ramipril tablets 5.0/5.0 mg

## PRESENTATION

Tazko 2.5/2.5 mg  
Apricot, circular, biconvex tablets 9 mm diameter engraved <sup>H</sup><sub>OD</sub> on one side and  
2.5 mg on the other

Tazko 5/5 mg  
Reddish-brown, circular, biconvex tablets, 9 mm diameter <sup>H</sup><sub>OE</sub> on one side and  
5 mg on other

Tazko tablets are a circular, biconvex, film coated two-layered tablet, with felodipine in an extended-release gel matrix formulation in one layer and rapidly dissolving ramipril in the other layer.

## USES

### ACTIONS

Tazko

The calcium antagonist felodipine and the ACE inhibitor ramipril both reduce blood pressure by vasodilatation. However, they have complementary mechanisms of action. Calcium antagonists dilate the arteriolar beds and the resulting vasodilatation and reduction of blood pressure may lead to activation of the sympathetic nervous system. ACE inhibitors reduce this sympathetic nervous system activation and block the renin angiotensin system. These complementary mechanisms of action underlie the additive antihypertensive response and the improved side-effect profile observed with combinations of calcium antagonists and ACE inhibitors. In particular, this balanced pattern of

Tazko® Data Sheet

vascular dilatation explains the attenuation of calcium antagonist-induced oedema.

The onset of the antihypertensive effect of a single dose of Tazko is 1-2 hours. The maximum antihypertensive effect occurs within 2-4 weeks and is maintained on long term therapy. The blood pressure reduction is even and effective throughout the 24 hour dosage interval.

Felodipine

Felodipine is a highly vascular selective calcium antagonist which lowers arterial blood pressure by decreasing vascular resistance. It exhibits a high degree of selectivity for smooth muscle in the arterioles and in therapeutic doses has no direct effect on cardiac contractility or conduction. Felodipine inhibits the electrical and contractile activity of vascular smooth muscles via an action at the cell membrane. Because of its lack of effect on venous smooth muscle and its adrenergic vasomotor control, felodipine does not cause orthostatic hypotension.

The renal vascular resistance is decreased by felodipine. Normal glomerular filtration rate is unchanged. In patients with impaired renal function glomerular filtration rate may be increased. Felodipine possesses a mild natriuretic/diuretic effect and therefore fluid retention does not occur.

Ramipril

Ramiprilat, the active metabolite of the prodrug ramipril, is a potent and long acting angiotensin-converting enzyme (ACE) inhibitor. In plasma and tissue, ACE catalyses the conversion of angiotensin I to the vasoconstrictor angiotensin II and also the breakdown of the vasodilator bradykinin. The vasodilatation induced by ramiprilat causes a reduction in blood pressure pre-load and after-load.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in the secretion of aldosterone. The latter decrease may result in a small increase in serum potassium. Ramipril causes a marked reduction in peripheral arterial resistance without major changes in renal plasma flow and glomerular filtration rate. In hypertensive patients, ramipril leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

Whilst the mechanism by which ramiprilat lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ramiprilat has an antihypertensive effect even in patients with low renin hypertension.

## PHARMACOKINETICS

### Tazko

In Tazko, the pharmacokinetics of felodipine, ramipril and ramiprilat are essentially unaltered from those of Agon<sup>®</sup> SR and Tritace<sup>®</sup> tablets. Felodipine does not influence the ACE inhibition caused by ramipril. The fixed combination tablets are thus regarded as bioequivalent to the free combination.

### Felodipine

Felodipine is completely absorbed from the gastrointestinal tract after administration, regardless of food intake. Peak plasma concentrations following administration are usually reached within 3-5 hours.

The systemic availability of felodipine is independent of dose in the therapeutic dose range. Due to pre-systemic metabolism of felodipine, the ability of Agon<sup>®</sup> SR is approximately 15%. Agon<sup>®</sup> SR produces a relatively flat plasma concentration versus time curve, minimising the post absorption peak seen with conventional tablets and maintaining therapeutic levels over the 24 hours following dosing. This permits single daily dosing of Agon<sup>®</sup> SR. Plasma concentrations are directly proportional to dose within the therapeutic dose range 2.5 mg- 10.0 mg.

The plasma protein binding of felodipine in man is approximately 99%. It is bound predominantly to the albumin fraction. In man, felodipine has a volume of distribution at steady state of approximately 10 L/kg.

Felodipine is extensively metabolised by the liver. All identified metabolites are inactive. Approximately 70% of a given dose is excreted as metabolites in the urine; the remaining fraction is excreted in the faeces. Less than 0.5% of a dose is recovered in unchanged urine.

Felodipine is a high clearance drug with an average blood clearance of 1200 mL/min. The average half-life of the terminal phase of the plasma

concentration time curve is 25 hours. There is no significant accumulation during long term treatment.

Average peak plasma concentrations of felodipine tend to be higher in elderly patients than in young healthy individuals.

The systematic availability, time to peak plasma concentration and volume of distribution do not appear to be significantly affected in patients with renal impairment.

Since there is often inter-individual variation in pharmacokinetic characteristics, dosage of felodipine for all patients should be individually adjusted rather than based only on patient's age.

### Ramipril

The prodrug ramipril undergoes extensive hepatic first-pass metabolism (hydrolysis) which is essential for the formation of ramiprilat, the sole active metabolite. In addition to this activation into ramiprilat, ramipril is glucuronized to form ramipril diketopiperazine (ester). After oral administration of ramipril, about 60% of the parent drug and its metabolites are eliminated in the urine and about 40% in the faeces. Less than 2% of the administered dose is recovered in the urine as unchanged ramipril. Approximately 80 to 90% of the metabolites in the urine and bile have been identified as ramiprilat or ramiprilat metabolites.

Following oral administration, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 56% and not significantly influenced by the presence of food in the GI tract. Peak plasma concentrations of ramiprilat are reached within 2 to 4 hours and the absolute bioavailability of ramipril and ramiprilat were 28% and 44% respectively, when 5 mg oral ramipril was compared with the same dose of IV ramipril.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose proportional. The 24 hour AUC for ramiprilat, however, is proportional to dose over the 2.5-20 mg dose range.

Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase, terminal elimination phase). The initial rapid decline, which represents distribution of the drug into a larger peripheral compartment and subsequent binding to both plasma and tissue ACE and

KININASE II, has a half-life of 2-4 hours. The effective half-life, which is relevant for dosage, is 13 to 17 hours under multiple dose conditions and the terminal phase with very low ramiprilat plasma concentrations has a half-life of approximately 4 to 5 days. This terminal phase is probably due to the slow dissociation of ramiprilat from ACE. After once daily doses, steady-state plasma concentrations are obtained by the fourth dose.

After IV administration, the systematic distribution volume of ramipril is approximately 90 L and the relative systemic distribution volume of ramiprilat is approximately 500 L. The protein binding of ramipril and ramiprilat is approximately 73% and 56% respectively.

Renal excretion of ramiprilat is reduced in patients with impaired renal function and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in patients with normal renal function.

When high doses (10 mg) of ramipril are administered, impairment of hepatic function retards the activation of ramipril into ramiprilat, resulting in increased ramipril plasma levels and delays the elimination of ramiprilat.

As in healthy subjects and patients with hypertension, there was also no relevant accumulation of ramipril and ramiprilat after oral administration of 5 mg ramipril once daily over two weeks in patients with congestive heart failure.

## **INDICATIONS**

For the treatment of hypertension in patients who are stabilised on a combination therapy of felodipine ER and ramipril, or in patients who have only partially responded to treatment with titrated monotherapy of either felodipine ER or ramipril and inclusion of either a calcium antagonist or ACE inhibitor was the next logical step.

## **DOSAGE AND ADMINISTRATION**

**Adults, including the elderly:** In general, treatment should be initiated with one Tazko 2.5/2.5 mg tablet daily. The dose may be increased if necessary after 2 to 4 weeks to one Tazko 5/5 mg tablet once daily.

Tablets must be swallowed whole. They must not be divided, crushed or chewed. They should be swallowed with a generous amount of liquid.

Tazko<sup>®</sup> Data Sheet

**Dosage recommendations for special patient groups if the existing treatment does not include ramipril or an ACE inhibitor:**

### **Patients on diuretics**

Consideration should be given to temporarily discontinuing the diuretic or at least reducing the dose 2 to 3 days before initiation of treatment with Tazko 2.5/2.5 mg. If this is not possible, start with ramipril 1.25 mg daily and increase to ramipril 2.5 mg daily before transferring to Tazko 2.5/2.5 mg.

### **Patients with incompletely corrected fluid or salt depletion**

Start with ramipril 1.25 mg daily and increase to ramipril 2.5 mg daily before transferring to Tazko 2.5/2.5 mg.

### **Patients with severe hypertension or those in whom a hypotensive reaction would constitute a particular risk**

Start with ramipril 1.25 mg daily and increase to ramipril 2.5 mg daily before transferring to Tazko 2.5/2.5 mg.

### **Patients with impaired renal function (creatinine clearance 20 to 50 mL/min)**

Start with ramipril 1.25 mg daily and increase to ramipril 2.5 mg daily before transferring to Tazko 2.5/2.5 mg daily. A maximum dose of 5 mg ramipril daily must not be exceeded.

## **CONTRAINDICATIONS**

- Hypersensitivity to felodipine, ramipril or any of the tablet excipients or any ACE Inhibitor.
- A history of angioneurotic oedema.
- In patients with haemodynamically relevant bilateral or, in the single kidney, unilateral renal artery stenosis
- Haemodynamically unstable patients
- Pregnancy or lactation

- Concomitant usage of ACE inhibitors and extracorporeal treatments leading to contact of blood with negatively charged surfaces. For example, dialysis with certain high flux membranes (e.g. polyacrylonitrile) or low density lipoprotein apheresis with dextran sulphate

## **WARNINGS AND PRECAUTIONS**

### **Patients with a significantly activated renin angiotensin system**

These patients are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or for the first time at an increased dose. They therefore need close blood pressure monitoring until no further acute reduction in blood pressure is expected. Significant activation of the renin angiotensin system is to be expected in patients with severe hypotension, patients with concomitant moderate heart failure, patients with haemodynamically relevant renal artery stenosis, patients on concomitant diuretic therapy or patients in whom fluid and salt depletion is present, including those who have suffered severe diarrhoea.

### **Patients at particular risk from pronounced reduction in blood pressure**

Patients with haemodynamically relevant stenosis of the coronary arteries or of the cerebral blood vessels will require careful monitoring in, preferably, a hospital or a similar setting.

### **Angioneurotic oedema**

Angioedema may involve the tongue, glottis or larynx. Emergency treatment of life-threatening angioneurotic oedema includes immediate adrenaline (SC or slow IV) with monitoring of ECG and blood pressure. Hospitalisation of the patient is advisable with observation for at least 12 to 24 hours and discharge only upon complete resolution of the symptoms.

### **Dialysis patients and those with a creatinine clearance below 20 mL/min**

No clinical experience on the use of TAZKO is available.

### **Use in the elderly**

It appears that age *per se* has relatively little impact on the pharmacokinetics of felodipine and ramipril, however liver and kidney function must be considered prior to their use.

### **Patients with severe impairment of liver function**

There is no experience in the use of Tazko in patients with severely impaired liver function. As both felodipine and ramipril are metabolised by the liver, it is recommended that treatment be initiated with low doses of felodipine or ramipril under close medical supervision.

### **Use in children**

Clinical data on the use of Tazko in children is not currently available, therefore use in this age group is not recommended.

### **Renal function**

It is recommended that renal function is monitored, particularly in the initial weeks of treatment with an ACE inhibitor. Careful monitoring is particularly required in patients with concomitant heart failure, renovascular disease, impairment of renal function and kidney transplant.

### **Potassium Monitoring**

Regular monitoring is recommended. Patients with impaired renal function require particularly close monitoring.

### **Haematological monitoring**

It is recommended that during ACE inhibitor therapy, the white blood cell count is monitored as agranulocytosis and bone marrow depression (including leukopenia/neutropenia) have been reported with ACE inhibitors. These have mostly occurred in patients with pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy or a combination of these factors.

### **Carcinogenicity**

Studies have been performed using felodipine in mice and rats. In the rat, interstitial cell tumours in the testes were observed, however this is a species specific effect caused by the endocrinological effect of felodipine in the rat. Such tumours were not found in mice.

Long term administration of ramipril to the rat and mouse did not show any tumorigenic effect. Renal tubules with oxyphilic cellular hyperplasia in rats are regarded as a response to functional alteration and morphological changes, and not as a neoplastic or preneoplastic response.

### **Mutagenicity**

Mutagenicity testing using 4 different tests have not revealed any mutagenic properties of felodipine,

Ramipril did not reveal any mutagenic or genotoxic effects in several test systems used.

### **Use in pregnancy**

Infants exposed to ACE inhibitors *in utero* must be closely monitored for hypotension, oliguria and hyperkalaemia. If oliguria is present or developing, support of blood pressure and renal perfusion may be necessary.

Tazko should not be taken during pregnancy. Pregnancy must be excluded before initiation of treatment and it must be avoided during treatment. If the patient intends to become pregnant, treatment with Tazko should be stopped and replaced by a treatment other than ACE inhibitors or calcium antagonists.

### **Use in Lactation**

Both felodipine and ramipril are excreted in breast milk. It is therefore recommended that Tazko is not given to nursing mothers.

### **Effect on the Ability to Drive and Use Machines**

Some undesirable effects (e.g. some symptoms of a reduction in blood pressure such as light-headedness, dizziness) may be accompanied by an impairment of the ability to concentrate and react. This may constitute a risk in situations where these abilities are of special importance e.g. driving a car or operating machinery.

## **ADVERSE EFFECTS**

Tazko

Generally, Tazko is well tolerated. Most adverse reactions reported in clinical trials were mild and were typical of reactions that can be expected from experience with the individual components, felodipine and ramipril. Experience in clinical trials indicates that TAZKO may result in a lower incidence of vasodilatation and peripheral oedema than with felodipine alone as well as a lower incidence of cough than with ramipril alone.

ACE inhibitors cause an increased likelihood and greater severity of anaphylactic and anaphylactoid reactions to other substances, or to, for example, insect bites.

The following list of adverse reactions and their frequencies are based upon experience with the monotherapies in their usual dosage range.

**Common (> 1%)**

**Uncommon ( $\leq$  1%)**

**Rare ( $\leq$  0.1%)**

**Very Rare ( $\leq$  0.1%)**

### **CARDIOVASCULAR**

Common	peripheral oedema, flushing (feeling of warmth), palpitations
Uncommon	those reactions attributable to a pronounced reduction in blood pressure including fatigue, dizziness, balance disorders, tinnitus, tachycardia
Rare	those reactions attributable to a pronounced reduction in blood pressure including arrhythmias, syncope, myocardial or cerebral ischemia, myocardial infarction, stroke
Very Rare	with ACE inhibitors, intensification or precipitation of Raynauds Phenomenon

### **RESPIRATORY**

Common	with ACE inhibitors, dry cough
Rare	with ACE inhibitors, nasal congestion, sinusitis, bronchitis, bronchospasm and dyspnoea

### **CNS**

Common	headache
Rare	nervousness, depressed mood, tremor, restlessness, visual and sleep disturbances, confusion and feelings of anxiety.
Very Rare	paresthesia

### **GASTROINTESTINAL**

Uncommon	nausea
Rare	vomiting, dryness of the mouth, glossitis, digestive disturbances, constipation, diarrhoea, abdominal

discomfort, inflammatory reactions of the oral cavity and gastrointestinal tract, gastric pain. With ACE inhibitors, increased levels of pancreatic enzymes. With felodipine gum hyperplasia, which can be avoided by careful dental hygiene.

Very Rare with ACE inhibitors, pancreatitis and ileus

#### **KIDNEY/ELECTROLYTE**

Uncommon with ACE inhibitors, increases in serum urea and creatinine

Rare with ACE inhibitors, increases in serum potassium

Very Rare increases in urinary outflow due to improved cardiac performance, decreases in serum sodium, impairment of renal function progressing to acute renal failure. ACE inhibitors may cause a deterioration of pre-existing proteinuria, though they usually improve this condition.

#### **ANAPHYLACTIC**

Uncommon mild angioneurotic oedema due to ACE inhibitor induced inhibition of kinin breakdown

Rare severe angioneurotic oedema due to ACE inhibitor induced inhibition of kinin breakdown. Angioneurotic oedema, other anaphylactic or anaphylactoid reactions due to felodipine, ramipril, or any of the other ingredients in TAZKO

#### **SKIN/MUCOUS**

Uncommon rash, pruritus, urticaria

Very Rare with ACE inhibitors, maculopapular rash, lichenoid, psoriasiform, exanthema and enanthema, erythema multiforme, Steven Johnson Syndrome, toxic epidermal necrolysis, alopecia, onycholysis. photosensitivity.

#### **HEPATIC**

Uncommon Increases in hepatic enzymes and/or serum bilirubin as well as cholestatic jaundice.

Very Rare with ACE inhibitors, liver damage. Liver damage is potentially fatal.

Tazko<sup>®</sup> Data Sheet

#### **HAEMATOLOGICAL**

Rare Mild reduction in haemoglobin content, and in the blood platelet, red blood cell and white cell count.

Very Rare Severe reduction in the blood platelet count. With ACE inhibitors, severe reduction in the red blood cell count and haemoglobin content (in isolated instances also due to haemolytic anaemia), severe reduction in the white cell count, agranulocytosis, bone marrow depression or pancytopenia.

Haematological reactions are more likely to occur in patients with impaired renal function, concomitant collagen disease (e.g. systemic lupus erythematosus or scleroderma) or in patients treated with drugs which alter the blood picture.

#### **OTHER**

Uncommon with ACE inhibitors, burning eyes

Rare impotence and reduced libido, muscle cramps, appetite loss, taste disturbances or loss.

Very Rare with ACE inhibitors, vasculitis, myalgia, fever and eosinophilia as well as raised antinuclear antibody titres, arthralgia

#### **INTERACTIONS**

##### **Enzyme P450 Inducers and Inhibitors**

Concomitant administration of substances which interfere with the cytochrome P450 system may affect plasma concentrations of felodipine. Enzyme inducers (e.g. phenytoin, carbamazepine, barbiturates) cause a decrease in plasma levels of felodipine. Enzyme inhibitors (e.g. cimetidine, erythromycin) have been shown to cause an increase in felodipine plasma levels.

##### **Grapefruit juice**

An increase in the bioavailability of dihydropyridines has been shown when they have been taken with grapefruit juice. The interaction is thought to be due to a bioflavonoid present in grapefruit juice.

### **Potassium supplements and potassium sparing diuretics**

Since ACE inhibitors may cause a rise in serum potassium, concurrent use of Tazko and potassium-sparing diuretics (e.g. spironolactone, amiloride, triamterene) or potassium supplements can increase the risk of hyperkalaemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored frequently.

### **High-flux dialyser membranes**

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux (e.g. polyacrylonitrile) membranes and low density lipoprotein apheresis with dextran sulfate have been reported to increase the risk of severe anaphylactoid reactions. The concomitant use of ACE inhibitors and such surfaces is therefore contraindicated (see CONTRAINDICATIONS).

### **Antihypertensive drugs**

Possible potentiation of the antihypertensive effect must be anticipated when Tazko is administered concurrently with other antihypertensives and other substances with antihypertensive potential (e.g. nitrates, tricyclic antidepressants, anaesthetics).

### **Lithium**

The excretion of lithium may be reduced by ACE inhibitors leading to lithium toxicity. Lithium levels must therefore be monitored.

### **NSAIDs**

As with other ACE inhibitors, the antihypertensive effects of ramipril may be decreased in patients taking NSAIDs. Furthermore, concomitant administration of ACE inhibitors and NSAIDs may exacerbate declining renal function and lead to an increase in serum potassium.

### **Antidiabetic agents**

The possibility of hypoglycaemia must be considered in patients treated concurrently with ramipril and antidiabetic agents.

### **Sympathomimetics**

These may reduce the antihypertensive effect of Tazko. Close blood pressure monitoring is recommended.

### **Food and Alcohol**

The absorption of Tazko is not influenced by food intake, however concomitant administration with alcohol may lead to increased vasodilatation. A high intake of dietary salt may decrease the antihypertensive effects of Tazko.

### **Desensitisation therapy**

ACE inhibitors may lead to an increased likelihood and greater severity of anaphylactoid and anaphylactic reactions. This must be considered when desensitisation is performed.

### **Tacrolimus**

Felodipine may increase the concentration of tacrolimus. When used together, the tacrolimus serum concentration should be followed and the tacrolimus dose may need to be adjusted.

### **Other**

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatic agents and other substances may change the blood picture. The likelihood of blood picture changes is increased when ramipril is administered with these substances.

## **OVERDOSAGE**

### **Symptoms**

Overdosage may cause excessive peripheral vasodilatation with marked hypotension and sometimes bradycardia, shock, electrolyte disturbances and renal failure.

### **Management**

Primary detoxification by, for example, gastric lavage, administration of adsorbents and/or sodium sulphate if possible during the first 30 minutes.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. In cases of accompanying bradycardia, atropine 0.5 - 1.0 mg should be administered intravenously. If this is not sufficient, plasma volume should be increased by electrolyte infusion (e.g. glucose, saline or dextran). Sympathomimetic drugs with predominant effect on the alpha adrenoreceptors or angiotensin II should be considered if the above-mentioned measures are insufficient.

### **FURTHER INFORMATION**

Inactive Ingredients: Hydroxypropyl methylcellulose, lactose anhydrous, maize starch pregelatinized, microcrystalline cellulose, sodium stearyl fumarate, hydroxypropylcellulose LF, polyoxyl 40 dehydrogenated castor oil, propyl gallate, sodium aluminium silicate, iron oxides E 172, paraffin, polyethylene glycol 6000, titanium dioxide E 171.

### **STORAGE AND SHELF LIFE**

3 years when stored below 25°C in PVC/PVDC blisters.

### **MEDICINE CLASSIFICATION**

Prescription Medicine

### **NAME AND ADDRESS**

Aventis Pharma Limited  
James & Wells Tower  
Part level 8  
56 Cawley Street  
Auckland, New Zealand

### **DATE OF PREPARATION**

7 May 2003