NEW ZEALAND DATA SHEET

DAPA-TABS

1. Product Name

DAPA-TABS 2.5 mg tablets.

2. Qualitative and Quantitative Composition

Each tablet contains 2.5 mg of indapamide hemihydrate.

DAPA-TABS contain lactose and traces quantities of sulphite and sugar (as galactose).

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

DAPA-TABS 2.5 mg tablets are 6.5mm, normal convex, pink, film coated tablet debossed "IE" over "2.5" on one side and "G" on the other.

Do not halve DAPA-TABS tablets.

4. Clinical Particulars

4.1 Therapeutic indications

Essential hypertension. It may be tried as a sole therapeutic agent in the treatment of mild to moderate hypertension. Normally indapamide is used as the initial agent in multiple drug regimens.

4.2 Dose and method of administration

Dose

One DAPA-TABS 2.5 mg tablet to be taken daily, by oral route, in the morning. The action of DAPA-TABS is progressive and whilst the optimum reduction in blood pressure is usually seen after four weeks, a further small but useful reduction in blood pressure may be observed over the following four to six weeks. A larger dose than one tablet (2.5 mg) of DAPA-TABS daily is not recommended as there is little additional antihypertensive effect, whilst the diuretic effect becomes more pronounced.

A single daily tablet of DAPA-TABS may effectively be combined with the following antihypertensive medicines: beta-blockers, methyldopa, clonidine, prazosin, and ACE inhibitors.

Combination with a diuretic is not recommended as significant electrolyte disturbances may occur. Indapamide has a slight but significant carry-over hypotensive effect lasting up to 1 or 2 weeks after the treatment is stopped.

Method of administration

Do not halve DAPA-TABS tablets.

4.3 Contraindications

- Severe renal failure, anuria, progressive and severe oliguria.
- Hepatic coma, hepatic encephalopathy or severe impairment of liver function.
- Known hypersensitivity to indapamide, other sulfonamide derivatives, or any of the excipients.
- Hypokalaemia.

4.4 Special warnings and precautions for use

Electrolyte changes

Electrolyte changes observed with indapamide become more pronounced at doses above 2.5 mg/day. The daily maximum recommended dose of DAPA-TABS is 2.5 mg administered as one tablet, since doses above 2.5 mg only increase the diuretic effect and electrolyte disturbances without any further appreciable antihypertensive effect.

Hypokalaemia

Hypokalaemia may occur at all doses. Symptoms of hypokalaemia include weakness, cramps, and cardiac dysrhythmias. Hypokalaemia is a particular hazard in patients treated with digoxin as dangerous or fatal arrhythmias may be precipitated. Although indapamide 2.5 mg can be safely administered to hypertensive patients with renal impairment, caution should be observed when it is administered to patients with severe renal impairment. In this case the unchanged drug is excreted primarily by the renal route, and plasma concentrations are elevated (see section 5.2).

Hepatic encephalopathy

When liver function is impaired, thiazide-related diuretics may cause, particularly in case of electrolyte imbalance, hepatic encephalopathy which can progress to hepatic coma. Administration of the diuretic must be stopped immediately if this occurs.

Uric acid

Hyperuricaemia may occur during treatment with indapamide, and gout has been reported rarely. Tendency to gout attacks may be increased in patients with hyperuricaemia.

Lithium

Diuretics should not be given with lithium because they reduce its renal clearance and add a high risk of lithium toxicity (see section 4.5).

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics. It is recommended to stop treatment if a photosensitivity reaction occurs during treatment. If re-administration of the diuretic is deemed necessary, it is recommended that areas exposed to the sun or to artificial UVA are protected.

Lactose intolerance

DAPA-TABS tablets contain lactose. Patients with an intolerance to lactose, rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Water and electrolyte balance

Patients receiving DAPA-TABS should be monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemia and hypokalaemia. Blood urea, nitrogen and uric acid should also be assessed during treatment.

The signs of electrolyte imbalance are dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, gastrointestinal disturbances such as nausea and vomiting, tachycardia and ECG changes.

Plasma sodium

This must be measured before starting treatment, then subsequently at regular intervals as treatment with any diuretic may cause hyponatraemia, sometimes with very serious consequences. The decrease in plasma sodium may initially be asymptomatic. Regular monitoring is therefore essential and should be more frequent in the elderly and in patients with cirrhosis (see sections 4.8 and 4.9). Treatment with any diuretic may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis.

Plasma potassium

Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. Hypokalaemia may cause muscle disorders. Cases of rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of hypokalaemia (<3.4 mmol/L) must be prevented in certain high risk populations, i.e. the elderly, malnourished and/or polymedicated, cirrhotic patients with oedema and ascites, and patients with coronary artery disease and/or heart failure. In these patients, hypokalaemia increases the cardiac toxicity of digitalis preparations and increases the risk of arrhythmias.

Hypokalaemia will be more common when combined with a steroid or adrenocorticotropic (ACTH) treatment and when electrolyte intake is inadequate. Individuals with a long QT interval, whether the origin is congenital or iatrogenic, are also at increased risk as hypokalaemia and bradycardia, are predisposing factors to the onset of severe arrhythmias, in particular, potentially fatal *Torsades de pointes*.

Plasma potassium should be measured in the first week of treatment. More frequent monitoring of plasma potassium is required in all the situations indicated above. Hypokalaemia, if detected, should be corrected.

Plasma calcium

Diuretic treatment should be withdrawn before the investigation of parathyroid function. Thiazide-related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When indapamide tablet is combined with other non-diuretic antihypertensive medicines, the effects on blood pressure are additive.

Sulfonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. Serious allergic skin reactions (such as Stevens-Johnson syndrome) have also occasionally been reported with sulfonamides. This should be considered when using indapamide.

Although indapamide dose of one 2.5 mg tablet/ day can be used safely in patients with hypertension and renal impairment, treatment should be discontinued if there is an increase in azotaemia and oliguria.

Studies in functionally anephric patients for one month undergoing chronic haemodialysis have not shown evidence of drug accumulation, despite the fact that indapamide is not dialysable.

A study in patients with impaired renal function demonstrated that patients with severe renal impairment (creatinine clearance 11-35 mL/min) had impaired clearance of indapamide and elevated plasma levels of the drug.

Severe hepatic disease

Caution should be used when treating patients with severe hepatic disease to avoid metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy. Treatment with the diuretic must be stopped immediately if this occurs.

Hypotension

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When indapamide is combined with other non diuretic antihypertensive medicines, the effects on blood pressure are additive.

Skin reactions

Sulfonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. Serious allergic skin reactions (such as Stevens-Johnson syndrome) have also occasionally been reported with sulfonamides. This should be considered when using indapamide.

Impaired renal function

Although a DAPA-TABS dose of one 2.5 mg tablet/day can be used safely in patients with hypertension and renal impairment, treatment should be discontinued if there is an increase in azotaemia and oliguria. Studies in functionally anephric patients for one month undergoing chronic haemodialysis have not shown evidence of drug accumulation, despite the fact that indapamide is not dialysable.

A study in patients with impaired renal function demonstrated that patients with severe renal impairment (creatinine clearance 11-35 mL/min) had impaired clearance of indapamide and elevated plasma levels of the drug.

Blood glucose

Monitoring of blood glucose is important in patients with diabetes, in particular in the presence of hypokalaemia.

Athletes

DAPA-TABS contains indapamide which may give a positive reaction in doping tests.

Chroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide, or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake 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.

Use in elderly

In the elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with DAPA-TABS when renal function is normal or only minimally impaired.

Use in children

Safety and effectiveness have not been established.

Interference with laboratory tests

Hyperuricaemia (0.4%). Hyperglycaemia (0.4%) (see section 4.8).

The following values represent the maximum variations from pre-treatment values in occasional patients at some stage during, but not necessarily throughout treatment. Blood uric acid up 8.6%, blood glucose up 6%, BUN up 5.7%, blood creatinine up 3.6%.

4.5 Interaction with other medicines and other forms of interaction

No interactions have been reported between indapamide and anticoagulants, or between indapamide and uricosuric medicines.

It is recommended that indapamide not be used in combination with a diuretic since the combination may cause hypokalaemia and hyperuricaemia.

Combinations that are not recommended

Lithium

The combined use of DAPA-TABS and lithium may result in increased plasma lithium levels and produce symptoms of overdose (due to decreased urinary lithium excretion). If diuretics are necessary, careful monitoring of plasma lithium and dose adjustment are required.

Combined use which requires special care

Torsades de pointes-inducing drugs

The combined use of indapamide and *Torsades de* pointes-inducing drugs, including the following, is not recommended due to the increased risk of ventricular arrhythmias, particularly *Torsades de pointes* (hypokalaemia is a risk factor). Medicines which induce *Torsades de pointes* include:

- Class Ia antiarrhythmics (e.g disopyramide) and classic Ic antiarrhythmic agents (e.g. flecainide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol)
- Some antipsychotics: phenothiazines (e.g. chlorpromazine, trifluoperazine), benzamides (e.g. amisulpride, sulpiride),butyrophenones (e.g. droperidol, haloperidol) and other antipsychotics
- Some antidepressants (e.g. citalopram, escitalopram)
- Antimicrobial agents: fluoroquinolones (e.g. moxifloxacin, ciprofloxacin), macrolides (e.g. erythromycin IV, clarithromycin), azole antifungal (e.g. fluconazole)
- Antiparasitics (e.g. chloroquine, pentamidine)
- Antihistamines
- Antiemetics (e.g. ondansetron, domperidone)
- Antineoplastic and immunomodulating agents (e.g. vandetanib, oxaliplatin, anagrelide)
- Anaesthetics
- Others: diphemanil, methadone, papaverine, cilostazol.

This list is indicative and not exhaustive.

Monitor (using plasma electrolytes and ECG) for hypokalaemia and correct, if required, before using DAPA-TABS and a *Torsades de pointes*-inducing drug in combination.

NSAIDs (systemic route) including COX-2 selective inhibitors, high dose salicylic acid (≥ 3 g/day)

Due to the risk of acute renal failure in patients with dehydration as a result of decreased glomerular filtration, it is recommended that hydration and renal function be monitored at the start of treatment.

Combined use with NSAIDs may also result in a reduction in the antihypertensive effect of DAPA-TABS.

Angiotensin converting enzyme (ACE) inhibitors

Combined use with ACE inhibitors in the presence of pre-existing sodium depletion (particularly in patients with renal artery stenosis) may increase the risk of sudden hypotension and/or acute renal failure.

In patients with hypertension when prior diuretic treatment may have caused sodium depletion, it is necessary to either:

- Stop the diuretic three days before starting treatment with the ACE inhibitor, and restart a hypokalaemic diuretic if necessary; or
- Give low initial doses of the ACE inhibitor and increase the dose gradually.

In patients with congestive heart failure, initiation with a very low dose of ACE inhibitor, possibly after a reduction in the dose of the hypokalaemic diuretic, is recommended.

The monitoring of renal function (plasma creatinine) during the first weeks of treatment with an ACE inhibitor is recommended in all patients.

Other compounds causing hypokalaemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), stimulant laxatives

Due to the increased risk of hypokalaemia (additive effect).

- Monitoring, and correction if required, of plasma potassium (especially during treatment with digoxin) is recommended.
- The use of non-stimulant laxatives is recommended.

Baclofen

Due to the increased risk of antihypertensive effects, it is recommended that hydration and renal function be monitored at the start of treatment.

Digoxin

Monitoring of plasma potassium and ECG is recommended due to the increased risk of hypokalaemia following co-administration of indapamide and digoxin.

Allopurinol

Combined use with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Combinations to be taken into consideration

Potassium-sparing diuretics (amiloride, spironolactone, triamterene)

Due to the increased risk of either hyperkalaemia or hypokalaemia (particularly in patients with renal failure or diabetes), care should be taken when co-administering potassium-sparing diuretics. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin

Do not co-administer with metformin when plasma creatinine exceeds 15 mg/L (135 µmol/L) in men and 12 mg/L (110 µmol/L) in women due to the increased risk of metformin induced lactic acidosis as a result of the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics.

Iodinated contrast media

Adequate hydration before administration of the iodinated compound is recommended due to an increased risk of acute renal failure resulting from dehydration, particularly when large doses of iodinated contrast media are used.

Imipramine-like antidepressants, neuroleptics

Caution is recommended with these combinations due to an increased antihypertensive effect and increased risk of orthostatic hypotension.

Calcium (salts)

Caution is recommended with this combination due to the risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

Ciclosporin, tacrolimus

Caution is recommended with this combination due to the risk of increased plasma creatinine without any change in circulating cyclosporin levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (tetracosactrin) (systemic route)

Caution is recommended with this combination due to the risk of decreased antihypertensive effect (water/sodium retention due to corticosteroids).

4.6 Fertility, pregnancy and lactation

Pregnancy

(Category C)

Indapamide should be avoided in pregnant women and should not be used to treat oedema in pregnancy.

There are limited data with the use of indapamide in pregnant women. Prolonged exposure to thiazides during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause foetal-placental ischaemia and growth retardation.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like furosemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy, medicines of this type should be used with caution and at the lowest effective dose.

Breast-feeding

Indapamide should not be used during breast feeding. Indapamide is excreted in human breast milk and the possible effect on the newborn is unknown and cannot be excluded. Indapamide is closely related to thiazide diuretics which have been associated with a decrease in, or even suppression of, lactation. Hypersensitivity to sulfonamide-derived medicines and hypokalaemia might occur.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

Indapamide does not affect vigilance but different reactions related to a decrease in blood pressure may occur in individual cases, especially at the start of treatment or when another antihypertensive agent is added. Treatment with any blood pressure lowering agent may, therefore, affect the ability to drive, cross the road safely or operate machinery.

4.8 Undesirable effects

In general, most adverse effects are mild and transient. The most frequently reported are hypersensitivity reactions, mainly dermatological (in subjects with a predisposition to allergic and asthmatic reactions and macropapular rashes), asthenia, dizziness, headache, fatigue, muscle

cramps and gastrointestinal disturbances. These usually occur within the first month of treatment. During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/L) was seen in 25% of patients and < 3.2 mmol/L in 10% of patients after four to six weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/L. Hypochloraemia 9.4%; hyponatraemia 3.1%.

The majority of adverse reactions concerning clinical or laboratory parameters are dose-dependent. Other adverse reactions have been non-specific. Cutaneous rash and impotence have been occasionally reported. Percentages shown below indicate the incidence in clinical trials.

The following undesirable effects have been observed with indapamide during treatment and are ranked according to the following frequencies: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

MedDRA system organ class	Adverse effects	Frequency
Blood and the lymphatic system disorders	Agranulocytosis	Very rare
	Aplastic anaemia	Very rare
	Haemolytic anaemia	Very rare
	Leucopenia	Very rare
	Thrombocytopenia	Very rare
Metabolism and nutrition disorders	Hypercalcaemia	Very rare
	Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see sections 4.3 and 4.4)	Not known
	Hyponatraemia† (see section 4.4)	Not known
Nervous system disorders	Vertigo	Rare
	Fatigue	Common
	Headache	Common
	Dizziness	Common
	Paraesthesia	Rare
	Syncope§	Not known
	Drowsiness	Uncommon
	Sleepiness	Uncommon
	Insomnia	Uncommon
	Anxiety	Uncommon
	Weakness	Uncommon

Eye disorders	Myopia§	Not known
	Blurred vision§	Not known
	Visual impairment	Uncommon
	Acute angle-closure glaucoma§	Not known
	Choroidal effusion§	Not known
Cardiac disorders	Arrhythmia	Very rare
	Torsades de pointes (potentially fatal) § (see sections 4.4 and 4.5)	Not known
	Palpitations	Very rare
	Chest pain	Very rare
Vascular disorders	Hypotension	Very rare
Gastrointestinal disorders	Vomiting	Uncommon
	Dyspepsia	Uncommon
	Abdominal pain	Uncommon
	Nausea	Rare
	Constipation	Rare
	Dry mouth	Rare
	Pancreatitis	Very rare
Hepatobiliary disorders	Abnormal hepatic function	Very rare
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency§ (see sections 4.3 and 4.4)	Not known
	Hepatitis§	Not known
Skin and subcutaneous tissue disorder	Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions	Common
	Maculopapular rashes	Common
	Purpura	Uncommon
	Pruritis	Uncommon
	Angioedema	Very rare
	Urticaria	Very rare

	Toxic epidermal necrolysis	Very rare
	Stevens-Johnson Syndrome	Very rare
	Possible worsening of pre-existing acute disseminated lupus erythematosus§	Not known
	Photosensitivity reactions§ (see section 4.4)	Not known
Musculoskeletal disorders	Muscle cramps	Common
	Muscle spasms§	Not known
	Muscular weakness§	Not known
	Myalgia§	Not known
	Rhabdomyolysis§	Not known
Renal and urinary disorders	Renal failure	Very rare
	Cystitis	Uncommon
Investigations	Electrocardiogram QT prolonged§ (see sections 4.4 and 4.5)	Not known
	Blood glucose increased§‡ (see section 4.4)	Not known
	Blood uric acid increased§‡ (see section 4.4).	Not known
	Elevated liver enzyme levels§	Not known

§Reported for indapamide as a post-marketing adverse effect.
‡Appropriateness of treatment with indapamide must be very carefully weighed in patients with gout or diabetes.
† Reported in clinical studies with the immediate release formulation of indapamide, and not seen in sustained release studies.

Other adverse reactions, reported in clinical studies with the immediate release formulation of indapamide include the following:

Central nervous system

Lethargy

Gastrointestinal

Anorexia, gastralgia, diarrhoea

Metabolism and nutrition disorders

Hypochloraemia, hyponatraemia

Musculoskeletal

Joint pain, back pain, weakness of legs

Cardiac disorders

Tachycardia, ECG changes (non-specific ST-T changes, U waves, left ventricular strain).

Vascular disorders

Orthostatic hypotension

Urogenital

Modification of libido, polyuria

Endocrine

Gout

Other

Tinnitus, malaise/fainting, sweat

Laboratory abnormalities

BUN increase, blood creatinine increase

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms

Signs of acute poisoning at higher doses take the form of water/electrolyte disturbances (hyponatraemia, hypokalaemia) and may include the possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia). In cirrhotic patients, an overdose might precipitate hepatic coma.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. Discontinue drug; induce emesis or perform gastric lavage and/or administration of activated charcoal (activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected), correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain, ATC code: C03BA11

Indapamide is a nonthiazide indole derivative of chlorosulfonamide.

Indapamide is a white crystalline lipophilic powder, soluble in methanol, ethanol, acetic acid and ethyl acetate, very slightly soluble in ether, chloroform and benzene and practically insoluble in water. Melting point is approximately 185°C.

Mechanism of action

Indapamide is an oral antihypertensive medicine. The mechanism whereby indapamide exerts its antihypertensive action has not been completely elucidated; both vascular and renal actions have been implicated.

At a dose of 2.5 mg, the renal effects of indapamide are minimal and the antihypertensive effect of indapamide has been attributed to a reduction in vascular reactivity to pressor amines. The finding that indapamide retains its antihypertensive activity in patients who are functionally anephric lends support to this hypothesis.

The renal site of action of indapamide is the proximal segment of the distal tubule. Indapamide appears to have natriuretic properties (sodium and chloride being excreted in equivalent amounts) with less effect on kaliuresis or uric acid excretion. Only at doses greater than 2.5 mg/day is an appreciable increase in urinary volume observed in man. No significant changes in plasma sodium levels have been observed in clinical studies. Significant hypokalaemia (plasma potassium <3.2 mmol/L) has been reported in some 10% of patients.

Indapamide hemihydrate 2.5 mg daily does not adversely affect serum triglycerides, LDL cholesterol, the LDL-HDL cholesterol ratio, or glucose tolerance.

5.2 Pharmacokinetic properties

Absorption

Possibly related to its high lipid solubility, absorption of indapamide from the gastrointestinal tract is rapid (within 0.5 to 1 hour after an oral dose) and complete. Bioavailability of the tablet formulation is 100% and is virtually unchanged with food or antacids.

Distribution

Indapamide is widely distributed throughout the body, with extensive binding to specific sites. In blood, it is highly bound to red blood cells (80%) and, more specifically, to carbonic acid anhydrase (98%) without having any significantly inhibiting activity on this enzyme.

In plasma, it is relatively highly bound to plasma proteins (79%). It is also taken up to a significant degree in the vascular compartment, the drug has a relatively low apparent volume of distribution (approximately 60 L) and 40% of the dose is located in the blood one hour after administration.

Biotransformation

Indapamide is extensively metabolised in the liver.

Elimination

After a single dose of 2.5 mg, as well as after repeated administration of 2.5 mg daily for 15 days, plasma elimination half-life of unchanged indapamide is biphasic with half-lives of 14 to 25 hours, indicating that once daily dosing is possible and that no change in kinetics occurs after repeated dosing. Both single and multiple dose data indicate that indapamide's kinetic are linear. Steady-state plasma levels are reached within three to four days after starting treatment and the drug does not accumulate in hypertensive patients with various degrees of renal insufficiency.

Following radioactivity studies using carbon-14, the main route of elimination is the urine, but only 5 to 7% of the dose is excreted into the urine as unchanged drug; 20 to 23% of total radioactivity is eliminated into the faeces. Renal clearance of indapamide (as unchanged drug) is approximately 5 mL/minute, representing less than 10% of systemic clearance.

The high lipid solubility of the indoline moiety confers to indapamide its highly localised binding to structures in the cardiovascular system.

Linearity/non-linearity

Both single and multiple dose data indicate that indapamide's kinetics are linear.

5.3 Preclinical safety data

Fertility

A reproductive toxicity study in rats showed no impairment of male or female fertility at oral indapamide doses up to 25 mg/kg/day, however, the number of implantation sites was reduced at the highest dose.

Carcinogenicity

Carcinogenicity studies in mice and rats showed no evidence of tumourigenicity when indapamide was administered in the diet at levels up to 100 mg/kg/day.

Mutagenicity

Indapamide was negative in mutagenicity tests in bacteria and bone marrow micronucleus tests in mice. There was a decrease in weight gain of the F1 generation from rats treated orally at 2.5 mg/kg/day. Galactopoiesis was affected in the F1 generation from rats treated orally at 0.5 mg/kg/day and this led to increased mortality of the F2 generation during the first 48 hours of life. No embryo-foetal toxicity or teratogenic potential were seen in rats (up to 150 mg/kg/day) and in rabbits (up to 180 mg/kg/day).

6. Pharmaceutical Particulars

6.1 List of excipients

DAPA-TABS tablet also contains:

- Sodium starch glycollate
- Magnesium stearate
- Cellulose microcrystalline
- Lactose anhydrous
- Croscarmellose sodium
- Opadry Pink OY-6953

DAPA-TABS are gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister pack - store at or below 30°C.

Bottle – store at or below 25°C.

6.5 Nature and contents of container

HDPE bottle with PP cap and cotton wool rope. Pack-sizes of 30 or 100 tablets.

Blister pack. Pack sizes of 30 or 90 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 0800 579 811

9. Date of First Approval

18 October 1990

10. Date of Revision of the Text

7 September 2020

Section	
2	Added excipients with known effects.
4.4	Added hepatic encephalopathy, chroidal effusion, acute myopia and secondary angle-closure glaucoma, and use in elderly as additional W&P. Additional W&P information on plasma potassium and plasma calcium to align with source.
4.5	Additional *Torsades de pointes* inducing agents added. Minor editorial changes.
4.8	Additional adverse effects added for eye disorders, musculoskeletal disorders and metabolism and nutrition disorders. Additional footnote.
5.2	Minor editorial changes.
6.1	Reorganized excipient list.
8	Updated sponsor contact phone number.