SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pamid Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.5 mg Indapamide
For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
tablet
White, convex, scored in one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Diuretic for the treatment of hypertension and fluid retention

4.2 Posology and method of administration
Oral use

Adults:
The dosage of one tablet, containing 2.5mg indapamide, to be taken daily in the morning.

Renal failure (see sections 4.3 and 4.4)
In severe renal failure (creatinine clearance below 30 ml/min), treatment is contraindicated.
Thiazides and related diuretics are fully effective only when renal function is normal or only minimally impaired.

Elderly (see section 4.4):
As for adults.
In the elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with indapamide when renal function is normal or only minimally impaired.

Hepatic impairment (see sections 4.3 and 4.4)
In severe hepatic impairment, treatment is contraindicated.

Children and adolescents:
Indapamide is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

The action of indapamide is progressive and the reduction of blood pressure may continue and not reach a maximum until several months after the start of therapy. A larger dose than 2.5mg indapamide daily is not recommended as there is no appreciable additional anti-hypertensive effect but a diuretic effect may become apparent. If a single daily tablet of indapamide does not achieve a sufficient reduction

in blood pressure, another antihypertensive agent may be added such as beta-blockers, ACE inhibitors, methyldopa, clonidine and other adrenergic blocking agents.
The co-administration of indapamide with diuretics which may cause hypokalaemia is not recommended.
There is no evidence of rebound hypertension on withdrawal of indapamide.

Pamid tablets are for oral administration only. Pamid tablets can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance, Sulphonamide derivatives or to any of the excipients listed in section 6.1.
- Severe renal failure
- Hepatic encephalopathy or severe impairment of liver function
- Hypokalaemia

4.4 Special warnings and precautions for use:

Special warnings:
Hepatic impairment:
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.

Excipients
Patients with rare heredity problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Photosensitivity
Cases of photosensitivity have been reported with thiazide and thiazide-related diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Special precautions for use:

- ***Water and electrolyte balance*:**
    - *Plasma sodium:*

This must be measured before starting treatment, then at regular intervals subsequently. Any diuretics treatment may cause hyponatremia, sometimes with very serious consequences. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be even more frequent in the elderly and cirrhotic patients (See sections 4.8 and 4.9).

    - *Plasma potassium:*

Potassium depletion with hypokalemia 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 hypokalemia (<3.4 mmol/l) must be prevented in certain high-risk populations, i.e. the elderly, malnourished and/or poly-medicated, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients.

In this latter situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias. Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a pre-disposing factor to the onset of severe arrhythmias, in particular, potentially fatal torsades de pointes.
More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement should be obtained during the first week following the start of treatment.
Detection of hypokalaemia requires its correction. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

- *Plasma magnesium:*

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result inhypomagnesaemia (see section 4.5 and 4.8).

- *Plasma calcium:*

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

- ***Blood glucose:***

Monitoring of blood glucose is important in diabetics, in particular in the presence of hypokalaemia.

- ***Uric acid:***

Tendency to gout attacks may be increased in hyperuricaemic patients.

- ***Renal function and diuretics:***

Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired (plasma creatinine below levels of the order of 25 mg/ml, i.e. 220 µmol/L in an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.
Hypovolaemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in blood urea and plasma creatinine. This transitory functional renal insufficiency is of no consequence in individuals with normal renal function but may worsen pre-existing renal insufficiency.

- ***Choroidal 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

- ***Athletes:***

The attention of athletes is drawn to the fact that this medicinal product contains an active ingredient, which may give a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations that are not recommended:

Lithium:

Increased plasma lithium with signs of overdose, as with a salt-free diet (decreased urinary lithium excretion). However, if the use of diuretics is necessary, careful monitoring of plasma lithium and dose adjustment is required.

Combinations requiring precautions for use

***Torsades de pointes-inducing drugs such as but not limited to:*:**

Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
Class III antiarrhythmics (amiodarone, bretylium, sotalol, dofetilide, ibutilide),

Some antipsychotics:

phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, Sultopride, tiapride), butyrophenones (droperidol, haloperidol), other antipsychotics (e.g. pimozide)

other substances: bepridil, cisapride, diphemanil, erythromycin IV, mizolastine, sparfloxacin, moxifloxacin, halofantrine, pentamidine, Terfenadine, vincamine IV, methadone, astemizole, Increased risk of ventricular arrhythmias, particularly Torsades de pointes (hypokalaemia is a risk factor).
Monitor for hypokalaemia and correct, if required, before introducing this combination. Clinical, plasma electrolytes and ECG monitoring.
Use substances which do not have the disadvantage of causing torsade de pointes in the presence of hypokalaemia.

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

Possible reduction in antihypertensive effect of indapamide.
Risk of acute renal failure in dehydrated patients (decreased glomerular filtration).
Hydrate the patient; monitor renal function at the start of treatment.

***Angiotensin converting enzyme (ACE) inhibitors*:**

Risk of sudden hypotension and/or acute renal failure when treatment with an ACE inhibitor is started in the presence of pre-existing sodium depletion (in particularl in individuals with renal artery stenosis).
In hypertension, when prior diuretic treatment may have caused sodium depletion, it is necessary:

- either to stop the diuretic 3 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 congestive cardiac failure, start with a very low dose of ACE inhibitor, possibly after a reduction in the dose of the concomitant hypokalaemic diuretic.
In all cases, monitor renal function (plasma creatinine) during the first weeks of treatment with an ACE inhibitor.

Other compounds causing hypokalaemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives:
Increased risk of hypokalaemia (additive effect).
Monitoring of plasma potassium and correction if required. Must be particularly borne in mind in case of concomitant digitalis treatment. Use non-stimulant laxatives.

Baclofen*:*
Increased antihypertensive effect.
Hydrate the patient; monitor renal function at the start of treatment.

Digitalis preparations:
Hypokalaemia predisposing to the toxic effects of digitalis.
Monitoring of plasma potassium, magnesium and ECG is recommended and, if necessary, adjust the treatment.

Combinations requiring special care:

Allopurinol:
Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Combinations which must be taken into consideration:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene):
Whilst rational combinations are useful in some patients, hypokalaemia or hyperkalaemia particularly in patients with renal failure or diabetes may still occur.
Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin:
Increased risk of metformin induced lactic acidosis due to the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics.
Do not use metformin when plasma creatinine exceeds 15 mg/liter (135 µmol/ L) in men and 12 mg/ L (110 µmol/ L) in women.

Iodinated contrast media:
In the presence of dehydration caused by diuretics, increased risk of acute renal failure, in particular when large doses of iodinated contrast media are used.
Rehydration before administration of the iodinated compound.

Imipramine-like antidepressants, neuroleptics:
Antihypertensive effect and increased risk of orthostatic hypotension increased (additive effect).

Calcium (salts):

Risk of hypercalcaemia resulting from decreased urinary calcium elimination.

Ciclosporin/ Tacrolimus:
Risk of increased plasma creatinine without any change in, circulating ciclosporin/ tacrolimus levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (systemic route):
Decreased antihypertensive effect (water/sodium retention due to corticosteroids)

4.6 Fertility, pregnancy and lactation
Pregnancy:
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of indapamide in pregnant women. Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a foeto-placental ischaemia and growth retardation.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of Indapamide during pregnancy.
Breast-feeding:
Indapamide is excreted in human milk in small amounts.
Hypersensitivity to sulfonamide-derived medicines and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded.
Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decreased or even suppression of milk lactation.
Indapamide is not recommended during breast-feeding.
Fertility:
Reproductive toxicity studies showed no effect on fertility in female and male rats (see section 5.3). No effects on human fertility are anticipated.

4.7 Effects on ability to drive and use machines
Indapamide does not affect vigilance but different reactions in relation with the decrease in blood pressure may occur in individual cases, especially at the start of the treatment or when another antihypertensive agent is added.
As a result, the ability to drive vehicles or to operate machinery may be impaired.

4.8 Undesirable Effects
Summary of safety profile
The most commonly reported adverse reactions are hypokalaemia, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

Tabulated summary of adverse reactions
The following undesirable effects have been observed with indapamide during treatment ranked under the following frequency:
Very common ($\geq$ 1/10); common ($\geq$ 1/100, < 1/10); uncommon ($\geq$ 1/1000, < 1/100); rare ($\geq$ 1/10000, < 1/1000), very rare ($\geq$ 1/100000, < 1/10000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable 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	Hypokalaemia (see section 4.4)	Common
	Hyponatraemia (see section 4.4)	Uncommon
	Hypochloraemia	Rare
	Hypomagnesaemia	Rare
	Hypercalcaemia	Very rare
Nervous System disorders	Vertigo	Rare
	Fatigue	Rare
	Headache	Rare
	Paraesthesia	Rare
	Syncope	Not known
Eye disorders	Myopia	Not known
	Blurred vision	Not known
	Visual impairment	Not known
	Acute angle-closure glaucoma	Not known
	Choroidal effusion	Not known
Cardiac Disorders	Arrhythmia	Very rare
	Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)	Not known
Vascular Disorders	Hypotension	Very rare
Gastrointestinal Disorders	Vomiting	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
Skin and Subcutaneous Tissue Disorder	Hypersensitivity reactions	Common
	Maculopapular rashes	Common
	Purpura	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
Renal and Urinary Disorders	Renal failure	Very rare

Musculoskeletal and Connective Tissue Disorders	Muscle spasms	Not known
	Muscular weakness	Not known
	Myalgia	Not known
	Rhabdomyolysis	Not known
Reproductive System and Breast Disorders	Erectile dysfunction	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

Description of selected adverse reactions
During phase II and III studies comparing indapamide 1.5mg and 2.5mg, plasma potassium analysis showed a dose-dependent effect of indapamide:
- Indapamide 1.5mg: Plasma potassium <3.4 mmol/l was seen in 10% of patients and <3.2 mmol/l in 4% of patients after 4 to 6 weeks treatment.
After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.
- Indapamide 2.5mg: Plasma potassium <3.4 mmol/l was seen in 25% of patients and <3.2 mmol/l in 10% of patients after 4 to 6 weeks treatment.
After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose
Symptoms:
Indapamide has been found free of toxicity up to 40 mg, i.e. 16 times the therapeutic dose.
Signs of acute poisoning take the form above all of water/electrolyte disturbances (hyponatraemia, hypokalaemia). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oligouria possibly to the point of anuria (by hypovolaemia).
Management:
Initial measures involve the rapid elimination of the ingested substance(s) by gastric wash-out and/or administration of activated charcoal, followed by restoration of water/electrolyte balance to normal in a specialized centre.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sulfonamides, plain;
ATC code: C03 BA11.
Indapamide is a non-thiazide sulphonamide with an indole ring, belonging to the diuretic family. At the dose of 2.5 mg per day indapamide exerts a prolonged antihypertensive activity in hypertensive human subjects.
Dose-effect studies have demonstrated that, at the dose of 2.5 mg per day, the antihypertensive effect is maximal and the diuretic effect is sub-clinical.
At this antihypertensive dose of 2.5 mg per day, indapamide reduces vascular hyperactivity to noradrenaline in hypertensive patients and decreases total peripheral resistance and arteriolar resistance.
The implication of an extrarenal mechanism of action in the antihypertensive effect is demonstrated by maintenance of its antihypertensive efficacy in functionally anephric hypertensive patients.
The vascular mechanism of action of indapamide involves:

- a reduction in the contractility of vascular smooth muscle due to a modification of transmembrane ion exchanges, essentially calcium;
- vasodilation due to stimulation of the synthesis of prostaglandin PGE_2 and the vasodilator and platelet antiaggregant prostacyclin PGI_2;
- potentiation of the vasodilator action of bradykinin.

It has also been demonstrated that in the short-, medium- and long-term, in hypertensive patients, indapamide:

- reduces left ventricular hypertrophy;
- does not appear to alter lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol;
- does not appear to alter glucose metabolism, even in diabetic hypertensive patients. Normalisation of blood pressure and significant reduction in microalbuminuria have been observed after prolonged administration of indapamide in diabetic hypertensive subjects.

Lastly, The co-prescription of indapamide with other anti-hypertensives (beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors) results in an improved control of hypertension with an increased percentage of responders compared to that observed with single-agent therapy.

5.2 Pharmacokinetic properties

Absorption
Indapamide is rapidly and completely absorbed after oral administration. Peak blood levels are obtained after 1-2 hours.
Distribution
Indapamide is concentrated in the erythrocytes and is 79% bound to plasma protein and to erythrocytes. It is taken up by the vascular wall in smooth
vascular muscle according to its high lipid solubility.
Elimination
70% of a single oral dose is eliminated by the kidneys and 23% by the gastrointestinal tract. Indapamide is metabolised to a marked degree with 7% of the unchanged

product found in the urine during the 48 hours following administration. Elimination half-life (ß phase) of indapamide is approximately 15 – 18 hours.

5.3 Preclinical safety data
Indapamide has been tested negative concerning mutagenic and carcinogenic properties.
The highest doses administered orally to different animal species (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The major symptoms of poisoning during acute toxicity studies with indapamide administered intravenously or intraperitoneally were related to the pharmacological action of indapamide, i.e. bradypnoea and peripheral vasodilation.
Reproductive toxicity studies have not shown embryotoxicity and teratogenicity.
Fertility was not impaired either in male or in female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose, maize starch, povidone 25, stearic acid, Hydroxypropyl-methylcellulose 2910, titanium dioxide, propylene glycol.

6.2 Incompatibilities
None stated

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C.
Store in the original package.

6.5 Nature and contents of container
Blister packs consisting of PVC and aluminium foil contained in a carton.
Pack sizes: 30 tablets.

6.6 Special precautions for disposal
None stated.

7 Marketing authorization holder and Manufacturer
CTS chemical industries Ltd.
Hakedma 3
Kiryat-Malachi
Israel

Revised in 07/2022 according to MOHs guidelines