Market Feasibility of Indapamide from View Point of a New Company

A thesis report submitted to the department of pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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APPROVAL

The research paper, entitled "Market feasibility of Indapamide from view point of a new company", submitted by Chowdhury Mohammad Sayem Sadly, ID no: 2005-2-70-002, to the Department of Pharmacy, East West University Bangladesh has been accepted as a satisfactory for the partial fulfillment of requirement of the degree of Bachelor of Pharmacy (B.PHRM) (Hon's). The Paper is also approved in its content & style.

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EWU LABORATORIES LTD.

Market Feasibility Report

Objective of Study

The objective of preparing this report is to find out whether Indapamide (an antihypertensive drug) could be launched in the market or not, from view point of new company.

1.0 Molecule information

Generic Name: Indapamide BP

Indication: Indapamide is a diuretic used for the treatment of hypertension (high blood pressure), alone or in combination with other antihypertensive drugs as well as for the treatment of salt and fluid retention associated with congestive heart failure or edema from pregnancy.[1]

High blood pressure adds to the workload of the heart and arteries. If it continues for a long time, the heart and arteries may not function properly. This can damage the blood vessels of the brain, heart, and kidneys resulting in a stroke, heart failure, or kidney failure. High blood pressure may also increase the risk of heart attacks. These problems may be less likely to occur if blood pressure is controlled.[2]

Indapamide works by preventing the kidney from reabsorbing (retaining in the body) salt and water that is destined to be eliminated in the urine. This results in increased urine output (diuresis). Indapamide also is thought to reduce the salt in the smooth muscle of the walls of blood vessels. (The salt ultimately is eliminated in the urine.) The loss of salt from the muscle causes the muscle to relax, and the relaxation of the vessels results in reduced blood pressure.[3]

2.0 Clinical Particulars[4]

2.1 Therapeutic indications

Essential hypertension.

2.2 Posology and method of administration

One tablet taken orally per 24 hours, preferably in the morning, to be swallowed whole with water and not chewed. At higher doses the antihypertensive action of indapamide is not enhanced but the saluretic effect is increased.

Renal failure:

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

Elderly:

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

Patients with hepatic impairment:

In severe hepatic impairment, treatment is contraindicated.

Children and adolescents:

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

2.3 Contraindications

- Hypersensitivity to indapamide, to other sulfonamides or to any of the excipients.

- Severe renal failure.

- Hepatic encephalopathy or severe impairment of liver function.

- Hypokalaemia.

2.4 Special warnings and precautions for use

Special warnings

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

Photosensitivity:

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

Excipients:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Special precautions for use

- Water and electrolyte balance:

• Plasma sodium:

This must be measured before starting treatment, then at regular intervals subsequently. Any diuretic treatment may cause hyponatraemia, 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.

• Plasma potassium:

Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. 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 edema and ascites, coronary artery disease and cardiac failure patients. In this 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 predisposing factor to the onset of severe arrhythmias.

More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be obtained during the first week following the start of treatment.

Detection of hypokalaemia requires its correction.

• Plasma calcium:

Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Hypercalcaemia may be due to previously unrecognised 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/l, 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 preexisting renal insufficiency.

- Athletes:

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

2.5 Interaction with other medicinal products and other forms of interaction

Combinations that are not recommended:

Lithium:

Increased plasma lithium with signs of overdosage, 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 are required.

Combinations requiring precautions for use:

Torsades de pointes-inducing drugs:

- class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),

- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide),

- some antipsychotics:

phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),

benzamides (amisulpride, sulpiride, sultopride, tiapride)

butyrophenones (droperidol, haloperidol)

others: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV.

Increased risk of ventricular arrhythmias, particularly torsades de pointes (hypokalaemia is a risk factor).

Hypokalaemia is monitored and corrected, if required, before introducing this combination. Clinical, plasma electrolytes and ECG monitoring.

Substances are used which do not have the disadvantage of causing torsades de pointes in the presence of hypokalaemia.

N.S.A.I.Ds. (systemic route) including COX-2 selective inhibitors, high dose salicylic acid (≥3 g/day):

Possible reduction in the antihypertensive effect of indapamide.

Risk of acute renal failure in dehydrated patients (decreased glomerular filtration). The patient is hydrated; renal function is monitored at the start of treatment.

Angiotensin converting enzyme (A.C.E.) inhibitors:

Risk of sudden hypotension and/or acute renal failure when treatment with an A.C.E. inhibitor is initiated in the presence of preexisting sodium depletion (particularly in patients 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 A.C.E. inhibitor, and restart a hypokalaemic diuretic if necessary;

- or to give low initial doses of the A.C.E. inhibitor and increase the dose gradually.

In congestive heart failure, it is better to start with a very low dose of A.C.E. inhibitor, possibly after a reduction in the dose of the concomitant hypokalaemic diuretic.

In all cases, renal function is monitored (plasma creatinine) during the first weeks of treatment with an A.C.E. inhibitor.

Other compounds causing hypokalaemia: amphotericin B, gluco-corticoids 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. Non-stimulant laxatives is used.

Baclofen:

Increased antihypertensive effect.

The patient to be hydrated; monitor renal function is monitored at the start of treatment.

Digitalis preparations:

Hypokalaemia predisposing to the toxic effects of digitalis.

Monitoring of plasma potassium and ECG and, if necessary, the treatment is adjusted.

Combinations to be taken into consideration:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene):

Whilst rational combinations are useful in some patients, hypokalaemia (particularly in patients with renal failure or diabetes) or hyperkalaemia 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/l (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 may be necessary 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 elimination of calcium.

Ciclosporin, tacrolimus:

Risk of increased plasma creatinine without any change in circulating cyclosporin levels, even in the absence of water/sodium depletion.

2.6 Pregnancy and lactation

Pregnancy:

As a general rule, the administration of diuretics should be avoided in pregnant women and should never be used to treat physiological edema of pregnancy. Diuretics can cause fetoplacental ischaemia, with a risk of impaired fetal growth.

Lactation:

Breast-feeding is inadvisable (Indapamide is excreted in human milk).

2.7 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.

2.8 Undesirable effects

The majority of adverse reactions concerning clinical or laboratory parameters are dose-dependent. Thiazide-related diuretics, including indapamide, may cause the following undesirable effects ranked under the following frequency:

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:

Very rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia

Nervous system disorders:

Rare: vertigo, fatigue, headache, paresthesia

Cardiac disorders:

Very rare: arrhythmia, hypotension.

Gastrointestinal disorders:

Uncommon: vomiting

Rare: nausea, constipation, dry mouth

Very rare: pancreatitis

Renal and urinary disorders:

Very rare: renal failure

Hepato-biliary disorders:

Very rare: abnormal hepatic function

Not known: possibility of onset of hepatic encephalopathy in case of hepatic insufficiency

Skin and subcutaneous tissue disorders:

Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions:

- Common: maculopapular rashes

- Uncommon: purpura

- Very rare: angioneurotic edema and/or urticaria, toxic epidermic necrolysis, Steven Johnson syndrome

Not known: possible worsening of pre-existing acute disseminated lupus erythematosus.

Cases of photosensitivity reactions have been reported.

2.9 Overdose

Any medication taken in excess can have serious consequences. Medical treatment should be sought immediately if an overdose is suspected. Indapamide has been found free of toxicity at up to 40 mg, i.e. 27 times the therapeutic dose.

Symptoms of Indapamide overdose may include Electrolyte imbalance (potassium or salt depletion due to too much fluid loss). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia).

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.

3.0 Pharmacological Properties[4]

3.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Phase II and III studies using monotherapy have demonstrated an antihypertensive effect lasting 24 hours. This was present at doses where the diuretic effect was of mild intensity.

The antihypertensive activity of indapamide is related to an improvement in arterial compliance and a reduction in arteriolar and total peripheral resistance.

Indapamide reduces left ventricular hypertrophy.

Thiazide and related diuretics have a plateau therapeutic effect beyond a certain dose, while adverse effects continue to increase. The dose should not be increased if treatment is ineffective.

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

- does not interfere with lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol;

- does not interfere with carbohydrate metabolism, even in diabetic hypertensive patients.

3.2 Pharmacokinetic properties

Indapamide 1.5 mg is supplied in a prolonged release dosage based on a matrix system in which the drug substance is dispersed within a support which allows sustained release of indapamide.

Absorption:

The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract.

Eating slightly increases the rapidity of absorption but has no influence on the amount of the drug absorbed.

Peak serum level following a single dose occurs about 12 hours after ingestion, repeated administration reduces the variation in serum levels between 2 doses. Intra-individual variability exists.

Distribution:

Binding of indapamide to plasma proteins is 79%.

The plasma elimination half-life is 14 to 24 hours (mean 18 hours).

Steady state is achieved after 7 days.

Repeated administration does not lead to accumulation.

Metabolism:

Elimination is essentially urinary (70% of the dose) and faecal (22%) in the form of inactive metabolites.

High risk individuals:

Pharmacokinetic parameters are unchanged in renal failure patients.

3.3 Preclinical safety data

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.

Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

4.0 Pharmaceutical Particulars [4]

4.1 List of excipients

Tablet:

Silica, colloidal anhydrous

Hypromellose

Lactose monohydrate

Magnesium stearate

Povidone

Film-coating:

Glycerol

Hypromellose

Macrogol 6000

Magnesium stearate

Tiatanium dioxide

4.2 Incompatibilities

Not applicable

4.3 Shelf life

2 years.

4.4 Special precautions for storage

Store below 30°C.

4.5 Nature and contents of container

10, 14, 15, 20, 30, 50, 60, 90, 100 tablets in blisters (PVC/aluminium).

Not all pack sizes may be marketed.

4.6 Special precautions for disposal and other handling

No special requirements

5.0 Prevalence and trend of the disease in Bangladesh

"The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7) provides an evidence-based approach to the prevention and management of hypertension. The key messages of this report are: in those older than age 50, systolic blood pressure (SBP) of >140 mmHg is a more important cardiovascular disease (CVD) risk factor than diastolic BP (DBP); beginning at 115/75 mmHg, CVD risk doubles for each increment of 20/10 mmHg; those who are normotensive at 55 years of age will have a 90 percent lifetime risk of developing hypertension; prehypertensive individuals (SBP 120–139 mmHg or DBP 80–89 mmHg) require health promoting lifestyle modifications to prevent the progressive rise in blood pressure and CVD; for uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes; this report delineates specific high-risk conditions, which are compelling indications for the use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel blockers); two or more antihypertensive medications will be required to achieve goal BP (<140/90 mmHg, or <130/80 mmHg for patients with diabetes and chronic kidney disease); for patients whose BP is >20 mmHg above the SBP goal or 10 mmHg above the DBP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered; regardless of therapy or care, hypertension will only be controlled if patients are motivated to stay on their treatment plan. Positive experiences trust in the clinician, and empathy improve patient motivation and satisfaction. This report serves as a guide, and the committee continues to recognize that the responsible physician's judgment remains paramount.[5]

According to the report "Prevalence of hypertension in Bangladesh: effect of socioeconomic risk factor on difference between rural and urban community" published in Bangladesh Medical Research Council bulletin 2002, the hypertension prevalence and related risks among native Bangladeshis are mention worthy. A total of 2,361 subjects over 20 years of age were investigated. Overall prevalence rates of systolic and diastolic hypertension in the study population were 14.4 and 9.1 percent respectively. The prevalence of systolic hypertension was significantly higher in rural than in urban participants. Compared with the poor the rich class had significantly higher prevalence of both systolic and diastolic hypertension. With increase of age, body mass index (BMI) and blood glucose level were

significantly related to hypertension; whereas the trend for increasing waist-to-hip ratio (WHR), adjusting for social class, was not significant. Regression analysis showed that age, BMI, rural area and rich class were the strong predictors for hypertension. This study explored that hypertension prevalence in the native Bangladeshis is almost comparable to that of other Asian populations and South Asian migrants.[6]

According to "The World Health Report 2004", main causes of mortality in Bangladesh are pneumonia, diarrhoea, respiratory failure, hypertension disease, accidental poisoning by others, pregnancy, malaria, Intra-cerebral and other health problems, acute myocardial infraction and anaemia. Among which 4.05% of all deaths occurs due to hypertension disease.[7]

6.0 Drugs available for the treatment of the disease

1. Angiotensin Converting Enzyme (ACE) Inhibitors
    - Captopril
    - Enalapril
    - Lisinopril
    - Perindopril
    - Ramipril
    - Benazepril
    - Fosinopril
    - Moexipril
    - Quinapril
    - Trandolapril
    - Bosentan

2. Angiotensin receptor blockers (ARB)
    - Losartan
    - Candesartan
    - Irbesartan
    - Telmisartan
    - Valsartan

3. Calcium Channel Blockers
    - Verapamil
    - Diltiazem
    - Nifedipine
    - Felodipine
    - Amlodipine
    - Nitrendipine
    - Isradipine
    - Nicradipine
    - Nisoldipine
    - Lacidipine

4. Diuretics

    I. Carbonic Anhydrase Inhibitors
        - Acetazolamide
        - Methazolamide
        - Dichlorphenamide

    II. High-Ceiling or Loop Diuretics
        - Furosemide
        - Bumetanide

    III. Thiazide and Thiazide-Like Diuretics
        - Chlorothiazide
        - Benzthiazide
        - Hydrochlorothiazide
        - Metolazone
        - Chlorthalidone
        - Indapamide
        - Xipamide
        - Clopamide

IV. Potassium-Sparing Diuretics

- Spironolactone
- Triamterene
- Amiloride

5. β Adrenergic Blockers
    - Propranolol
    - Nadolol
    - Pindolol
    - Carteolol
    - Timolol
    - Levobunolol
    - Sotalol
    - Metipranolol
    - Metoprolol
    - Atenolol
    - Acebutolol
    - Betaxolol
    - Bisoprolol
    - Esmolol

1. β + α Adrenergic Blockers
    - Labetelol
    - Carvedilol

2. α Adrenergic Blockers
    - Prazosin
    - Terazosin
    - Doxazosin
    - Phentolamine
    - Phenoxybenzamine

3. Central Sympatholytics
    - Clonidine
    - Methyldopa

4. Vasodilators
    - Hydralazine
    - Minoxidil
    - Diazoxide
    - Sodium Nitroprusside

7.0 Clinical advantage of the proposed product (in terms of efficacy, safety, convenience, pharmacokinetic profile, etc.)

	Indapamide SR
Efficacy and convenience	1. Indapamide 1.5 mg SR (sustained release formulation) allows the antihypertensive efficacy with a better acceptability profile. Indapamide has a dual mechanism of action: diuretic effect at the level of the distal tubule in the kidney and a direct vascular effect, both of which contribute to the antihypertensive efficacy of the drug. The SR formulation contains a hydrophilic matrix, which delivers a smoother pharmacokinetic profile. This avoids unnecessary plasma peak concentrations, which may be associated with side effects. 2. Indapamide SR has now been extensively used in hypertensive patients, including those at increased risk, for example elderly or diabetic patients. 3. It has been shown to decrease BP, particularly SBP (systolic blood pressure), with 24-h efficacy, allowing a once-daily dosage. Studies have demonstrated BP lowering to be at least as effective as all major therapeutic classes including the more recent antihypertensive drugs. 4. The treatment with indapamide SR results in a better or equivalent control of systolic blood pressure (SBP) than treatment with a standard dose of a true thiazide diuretic (hydrochlorothiazide), a

	calcium channel blocker (amlodipine) and an ACE inhibitor (enalapril). 5. Beyond BP decrease, indapamide SR has also been shown to protect against hypertensive target-organ damage in the heart and the kidney and to have a favorable metabolic profile. A broad evidence-base has accumulated to support the benefit of indapamide 1.5 mg SR in hypertensive patients, alone or as part of combination therapy, as recommended by the majority of guidelines.[8]

	Indapamide SR
Pharmacokinetic profile	1. Indapamide is rapidly and completely absorbed after oral administration. Peak blood levels are obtained after 1 to 2 hours. Indapamide is concentrated in the erythrocytes and is 79% bound to plasma proteins and to erythrocytes. 2. It has an elimination t½ of 16 hours. Seventy per cent of a single oral dose is eliminated by the kidneys and 23% by the gastrointestinal tract. Indapamide is metabolized to a marked degree, the unchanged product representing approximately 5% of the total dose found in the urine during the 48 hours following administration. 3. The methyl-indoline portion of the molecule gives indapamide its lopiphilic character, and indapamide's lipid solubility is 5 to 8 times that of the thiazides. Indapamide is taken up by the vascular wall of smooth vascular muscle according to its high lipid solubility. It is this highly localized distribution, in contrast to compounds which concentrate in urine, which may account for the observed differences in the pharmacological and clinical activity of the drug.[10]

	Indapamide SR
Side effects	1. Indapamide SR is devoid of the well-known diuretic-associated metabolic adverse events. Renal function, as assessed by the determination of urea and creatininaemia, remained unaffected after short and long-term therapy with indapamide SR.[11] 2. It has been proven to have a neutral effect both on lipid and glucose profiles. 3. The main adverse effects of thiazides are the result of some of the renal actions, K^+ depletion being the most important. Others are metabolic alkalosis and increased plasma uric acid. Indapamide has little obvious effect on K^+, uric acid and glucose excretion. 4. Electrolyte disturbances and K^+ loss are minimal at antihypertensive doses.[12]

8.0 Market Analysis:

Data Source: IMS *Period:* 2007, 2nd quarter

8.1. Market Overview:

Therapeutic Class: Antihypertensive

Sub-Therapeutic Class: Diuretic (Thiazide Type)

Therapeutic Class/Sub-Class	Year 2005			Year 2006			Year 2007		
	Market Size in BDT	Share (%)	Growth (%)	Market Size in BDT	Share (%)	Growth (%)	Market 0Size in BDT	Share (%)	Growth (%)
Cardiovascular System	1,995,312,252	6.78	20.60	2,381,152,780	6.48	19.34	2,738,141,900	7.25	14.99
Diuretics	147,219,104	7.38	24.21	165,362,967	6.94	12.32	194,930,154	7.12	17.88
Thiazides	51,749,098	35.15	56.75	53,547,634	32.38	3.48	68,389,314	35.08	27.72
Indapamide	47,062,196	90.94	62.55	48,195,534	90.00	2.41	63,510,127	92.87	31.78

Comments

From the above chart it could be easily figured out that the sales of cardiovascular drugs (therapeutic class) is increasing every year. The same statement is also applicable for the diuretics (sub therapeutic class) especially thiazide diuretics, which demonstrate a continuously increasing high growth rate. Indapamide as a molecule itself is enjoying healthy market share among the thiazide type diuretics which sales can also be characterized by persistent escalating growth.

8.2 Competitive Market Situation:

8.2.1 Direct Competitor

Indapamide (plain)

Brand/ Product	Company	Year 2005			Year 2006			Year 2007		
		Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)
Natrilix	SVR	34,001,450	72.25	23.74	30,825,682	63.69	-9.34	33,335,009	52.49	8.41
Hypen-SR	OPI	12,695,544	26.98	761.55	14,446,773	29.98	13.79	21,287,835	33.52	47.35
Repres	SQA	365,203	0.78	999.00	6,591,333	6.07	700.40	6,591,333	10.98	125.49
Micturex	ORN	0	0.00	0.00	0	0.00	0.00	1,181,733	1.86	999.00
Indapa	D-I	0	0.00	0.00	0	0.00	0.00	1,114,216	1.75	999.00

Indapamide combination

Brand/ Product	Company	Year 2005			Year 2006			Year 2007		
		Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)
Indapril	IAP	3,197,484	67.59	999.00	9,798,938	52.50	206.46	8,951,496	46.38	-8.65
Perindal Plus	OPI	1,320,052	27.90	999.00	5,062,830	27.12	283.53	4,590,865	23.78	-9.32
Repres Plus	SQA	0	0.00	0.00	608,127	3.26	999.00	2,578,673	13.36	324.04
Pendoril Plus	RTA	193,295	4.09	999.00	2,026,424	10.86	948.36	1,698,569	8.80	-16.18
Inopil Plus	DLT	19,730	0.42	999.00	736,987	3.95	999.00	632,849	3.28	14.13
Midopril	GNR	0	0.00	0.00	241,511	1.29	999.00	501,065	2.60	107.47
Induric Plus	BXM	0	0.00	0.00	0	0.00	0.00	290,439	1.50	999.00
Dorin	ESF	0	0.00	0.00	190,777	1.02	999.00	57,696	0.30	-69.76

Data Source: IMS *Period:* 2007, 2nd quarter

8.2.2 Indirect Competitor (Other Diuretics)

Brand/ Product	Company	Year 2005			Year 2006			Year 2007		
		Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)
Lasix (Furosemide)	S.A	8,784,381	76.17	7.50	8,431,135	74.77	-4.02	10,913,094	76.65	29.44
Fusid (Furosemide)	SQA	2,003,781	17.37	8.40	2,346,690	20.81	17.11	2,975,420	20.90	26.79
Frusin (Furosemide)	OPI	557,775	4.84	-32.01	430,518	3.82	-22.82	326,882	2.30	-24.07
Dirusid (Furosemide)	DLT	3,501	0.03	999.00	21,962	0.19	527.31	10,413	0.07	-52.59
Trofurit (Furosemide)	MPX	12,418	0.11	-55.43	1,951	0.02	-84.29	8,970	0.06	359.76
Uratic (Furosemide)	DOC	0	0.00	-100.00	3,463	0.03	999.00	3,144	0.02	-9.21
Frusix (Furosemide)	GCO	9,976	0.09	-58.95	0	0.00	-100.00	0	0.00	0.00
Renalix (Furosemide)	A D	14,288	0.12	999.00	0	0.00	-100.00	0	0.00	0.00
Urex (Furosemide)	JAL	147,176	1.28	-19.84	40,616	0.36	-72.40	0	0.00	-100.00
Acuren (Hydrochlorothiazide)	IAP	4,160,525	88.77	10.43	4,812,561	89.92	15.67	4,325,441	88.65	-10.12
HTZ (Hydrochlorothiazide)	UNM	526,377	11.23	79.96	539,539	10.08	2.50	553,745	11.35	2.63
Tomide (Torasemide)	ACM	438,132	40.22	-44.69	282,695	44.32	-35.48	119,221	58.48	-57.83
Dilast (Torasemide)	IAP	456,635	41.91	-79.11	265,766	41.67	-41.80	52,710	25.85	-80.17
Luretic (Torasemide)	D-I	194,704	17.87	2.71	89,374	14.01	-54.10	31,938	15.67	-64.26

Data Source: IMS *Period:* 2007, 2nd quarter

Brand/ Product	Company	Year 2005			Year 2006			Year 2007		
		Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)
Verospirone (Spironolactone)	MPX	3,900,760	62.83	-9.58	4,440,495	67.07	13.84	5,508,736	86.34	24.06
Aldactone A (Spironolactone)	SEA	2,307,509	37.17	21.98	2,180,513	32.93	-5.50	871,797	13.66	-60.02
Acemox (Acetazolamide)	ACM	1,380,376	100.00	26.65	1,639,251	100.00	18.75	1,591,616	100.00	-2.91

Indirect Competitor (Other Diuretic Combinations)

Brand/ Product	Company	Year 2005			Year 2006			Year 2007		
		Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)
Frulac (Furosemide +Spironolactone)	ORN	29,955,107	43.51	-6.14	37,711,864	48.36	25.89	44,278,215	44.88	17.41
Edeloss (Furosemide +Spironolactone)	IAP	10,827,250	15.73	27.70	12,735,831	14.81	17.63	13,792,916	13.98	8.30
Diretic (Furosemide +Spironolactone)	D-I	5,545,444	8.06	114.89	6,698,330	7.79	20.79	8,288,717	8.40	23.74
Fusid Plus (Furosemide +Spironolactone)	SQA	0	0.00	0.00	4,445,331	5.17	999.00	6,766,202	6.86	52.21
Edeloss Plus (Furosemide +Spironolactone)	IAP	3,191,043	4.64	999.00	5,634,446	6.55	76.57	6,746,524	6.84	19.74

Data Source: IMS *Period:* 2007, 2nd quarter

Brand/ Product	Company	Year 2005			Year 2006			Year 2007		
		Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)
Edemide (Furosemide +Spironolactone)	ACM	9,050,654	13.15	28.28	8,980,481	10.44	-0.78	3,562,894	3.61	-60.33
Lasilactone (Furosemide +Spironolactone)	SA	0	0.00	0.00	0	0.00	0.00	2,038,227	2.07	999.00
Laxur (Furosemide +Spironolactone)	H9P	0	0.00	0.00	0	0.00	0.00	1,004,698	1.02	999.00
Fruselac (Furosemide +Spironolactone)	ATP	1,696,484	2.46	303.69	1,320,682	1.54	-22.15	879,236	0.89	-33.43
Furo Plus (Furosemide +Spironolactone)	BAC	0	0.00	0.00	0	0.00	0.00	688,633	0.70	999.00
Lasilactone (Furosemide +Spironolactone)	SA	0	0.00	0.00	0	0.00	0.00	2,038,227	2.07	999.00
Laxur (Furosemide +Spironolactone)	H9P	0	0.00	0.00	0	0.00	0.00	1,004,698	1.02	999.00
Fruselac (Furosemide +Spironolactone)	ATP	1,696,484	2.46	303.69	1,320,682	1.54	-22.15	879,236	0.89	-33.43
Furo Plus (Furosemide +Spironolactone)	BAC	0	0.00	0.00	0	0.00	0.00	688,633	0.70	999.00

Data Source: IMS

Period: 2007, 2nd quarter

Brand/ Product	Company	Year 2005			Year 2006			Year 2007		
		Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)	Value in BDT	Share (%)	Growth (%)
Spiromide (Furosemide +Spironolactone)	SEA	2,527,682	3.67	-50.01	1,693,049	1.97	-33.02	632,777	0.64	-62.63
Dirusid Plus (Furosemide +Spironolactone)	DLT	12,187	0.02	999.00	599,685	0.70	999.00	621,526	0.63	3.64
Dirucom (Furosemide +Spironolactone)	PPH	0	0.00	0.00	397,891	0.46	999.00	578,319	0.59	45.35
Tonemide (Furosemide +Spironolactone)	PAC	0	0	0.00	23,740	0.03	999.00	268,426	0.27	999.00
Redema (Furosemide +Spironolactone)	R7G	0	0.00	0.00	0	0.00	0.00	229,498	0.23	999.00
Freflo (Furosemide +Spironolactone)	SQA	2,142,343	3.11	999.00	44,632	0.05	-97.92	10,921	0.01	-75.53
Amizide (Hydrochlorothiazide+Amiloride)	SA	3,444,785	53.96	-20.64	2,911,803	51.50	-15.47	2,806,270	51.42	-3.62
Kaltide (Hydrochlorothiazide+Amiloride)	A-I	967,879	15.16	-5.15	684,409	12.10	-29.29	423,974	7.77	-38.05
Dezide (Hydrochlorothiazide+Triamterene)	ESF	1,971,411	30.88	-21.37	2,057,855	36.40	4.38	2,227,190	40.81	8.23

8.3 Price of the leading Products:

Brand	Company	Product	Pack Size	Price/Pack
Natrilix SR	Servier	Indapamide 1.5 mg	3x10's	Tk. 264.00
Repres SR	Square	Indapamide 1.5 mg	3x10's	Tk. 150.00
Repres Plus 2		Indapamide 0.625 mg + Perindopril 2 mg	3x10's	Tk. 210.00
Repres Plus 4		Indapamide 1.25 mg + Perindopril 4 mg	2x10's	Tk. 240.00
Hypen SR	Opsonin	Indapamide 1.5 mg	3x10's	Tk. 150.00
Indapa	Drug International	Indapamide 1.5 mg	5x10's	Tk. 250.00
Micturex	Orion	Indapamide 1.5 mg	3x10's	Tk. 150.00
Indapril 2	Incepta	Indapamide 0.625 mg + Perindopril 2 mg	3x10's	Tk. 210.00
Indapril 4		Indapamide 1.25 mg + Perindopril 4 mg	2x10's	Tk. 240.00
Induric Plus	Beximco	Indapamide 0.625 mg + Perindopril 2 mg	3x10's	Tk. 209.00
Pendoril Plus	Renata	Indapamide 0.625 mg + Perindopril 2 mg	1x10's	Tk. 120.00

8.4 Launching year of different Indapamide Brands in Bangladesh:

Brand	Company	Product	Launching Year
Natrilix	Servier	Indapamide 1.5 mg	2002
		Indapamide 2.5 mg	
Hypen SR	Opsonin	Indapamide 1.5 mg	2004
Repres	Square	Indapamide 1.5 mg	2005
Micturex	Orion	Indapamide 1.5 mg	2007
Indapa	Drug International	Indapamide 1.5 mg	2007
Indapril	Incepta	Indapamide 0.625 mg + Perindopril 2 mg	2005
		Indapamide 1.25 mg + Perindopril 4 mg	
Perindal Plus	Opsonin	Indapamide 0.625 mg + Perindopril 2 mg	2005
		Indapamide 1.25 mg + Perindopril 4 mg	
Repres Plus	Square	Indapamide 0.625 mg + Perindopril 2 mg	2006
		Indapamide 1.25 mg + Perindopril 4 mg	
Pendoril Plus	Renata	Indapamide 1.25 mg + Perindopril 4 mg	2005
Inopil Plus	Delta	Indapamide 1.25 mg + Perindopril 4 mg	2005
Induric Plus	Beximco	Indapamide 0.625 mg + Perindopril 2 mg	2007
Dorin	SK+F	Indapamide 0.625 mg + Perindopril 2 mg	2006
		Indapamide 1.25 mg + Perindopril 4 mg	

9.0 Dosage forms/Strengths available in World/Domestic market:

Indapamide:

Dosage Form	World Market	Domestic Market
	Strength	
Immediate release Tablet	1.5 mg, 2.5 mg	1.5 mg, 2.5 mg
Sustained release Tablet	1.5 mg	1.5 mg
Combination Preparation (Indapamide + Perindopril)	Indapamide 0.625 mg + Perindopril 2 mg	Indapamide 0.625 mg + Perindopril 2 mg
	Indapamide 1.25 mg + Perindopril 4 mg	Indapamide 1.25 mg + Perindopril 4 mg

10.0 Recommended (usual) Dose(s) of the Drug:

ADULTS

High Blood Pressure

The usual starting dose is 1.25 milligrams as a single daily dose taken in the morning. If it does not seem to be working, the dose may be increased up to 5 milligrams taken once a day.

Fluid Buildup in Congestive Heart Failure

The usual starting dose is 2.5 milligrams as a single daily dose taken in the morning. The dose may be increased to 5 milligrams taken once daily.[9]

CHILDREN

Studies on this drug have been done only in adult patients, and there is no specific information comparing use of indapamide in children with use in other age groups.[2]

11.0 Proposed Dosage forms/Strengths Strategy:

Dosage Form and Strength	Comment
Indur SR (Proposed Brand Name) (Indapamide 1.5 mg sustained release tablet)	Promotion highlighting its improved efficacy over other antihypertensive classes such as Calcium channel blockers (e.g. Amlodipine), ACE inhibitors (e.g. enalapril), in mild to moderate hypertensive patient as well as pregnant women suffering from edema.
Perindur (Proposed Brand Name) (Indapamide 1.25 mg + Perindopril 4 mg)	To meet the higher dosage requirement in serious hypertensive patients. Since combination gives synergistic effect, now-a-days more physicians tend to prescribe combination preparation. So generating prescriptions would not be a difficult task if vigorous promotion is carried out.

12.0 Business Expectation (along with assumptions)

In order to portrait a sales forecast, first prevalence of the disease (i.e. hypertension) needs to be considered. In a third world country like Bangladesh it's really difficult to get reliable data regarding the accurate number of patient suffering from hypertension. According to US Census Bureau, International Data Base, 2007, the prevalence extrapolations of hypertension is as follows:[13]

Population estimated used: 141,340,476

Extrapolated Prevalence: 25,981,704

Extrapolated Undiagnosed Prevalence: 7,794,511

Extrapolated diagnosed prevalence: 18,187,193

If the market growth of indapamide for past three years is studied, the average growth of the product can be upto 32% (approx.). Now if the market really grows by the assumed percentage then next year the total sale will increase by 20,323,240 BDT than the previous year. That means a total sale of next year will be 83,833,367 BDT. Without making any competition with the five leading brands if we target only 1.5% market share then our Expected sales value become 1,257,500 BDT.

Since hypertension is a life long disease and incase of indapamide once daily dose is sufficient, it should be available in a convenient pack containing thirty tablets (10's x 3) in order to meet the whole month requirement of the patient. The price of the local brands ranges from 5-7 Tk. Since the market is highly competitive, it would not be wise to exceed the range. We may set the price of our product 5 Tk. Per tablet i.e. 150 Tk. Per pack. So to achieve our sales target we have to sell at least 8383 pack of indapamide. If we presume that only 5% of the extrapolated diagnosed prevalence is the potential customers (909,359) then a demand of 909359 pack indapamide would be generated. So it could be said that our target is very much reachable. Since Indapamide market is growing extensively day by day, our sales might even exceed our expectation.

Expected Value (in Tk.): 1,257,500

Market Share: 1.5%

Expected Unit (Pack) to be sold: 8400

13.0 Comments on market potentiality

I would like to propose to launch Indapamide 1.5 mg sustained release tablet considering the following issues-

- To meet the requirement of hypertensive patients especially elderly patients or patients with target-organ damage, left ventricular hypertrophy (LVH) or with type II diabetes with microalbuminuria. Also to relieve salt and fluid retention during pregnancy.

- There are only few competitors in Indapamide tablet (1.5 mg sustained release) market. So it will be easier to penetrate the market and snatch a significant share. More over, by introducing it we can make our product as a complete brand with all strength.

- Better convenience for patients since it provides antihypertensive action with 24-hour efficacy, allowing a once-daily dosage.

- Market size of Indapamide molecule is increasing continuously.

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