FLUID MANAGER SUPPLEMENTS

SAFETY & PERFORMANCE SUMMARY

HB BIOTECHNOLOGIES CORPORATION

These statements not evaluated by the Food and Drug Administration. This product not intended to diagnose, treat, cure, or prevent any disease.

How It Works

Fluid Manager Supplements are clinically proven to absorb fluid from the body via the gastrointestinal route. The product works independently of kidney function and removes fluid from the body whether or not a person has functioning kidneys. It provides a method and process for dialysis free fluid management.

The superabsorbent material in **Fluid Manager Supplements** absorbs up to 65 times its weight in fluid. An increase in fecal volume with a decrease in urinary volume demonstrates the product is managing fluid.

Because the supplement transforms into a gel after absorbing fluid in the stomach, it also reduces feelings of hunger.

A strategy to manage fluid in real time could be useful all along the chronic kidney disease spectrum.

The product is not meant as a replacement for dialysis. However, fluid overload in between dialysis treatments is a common complication, affecting up to 40% or more of dialysis patients.

Use of **Fluid Manager Supplements** may provide value to numerous populations that experience excess fluid retention or edema.

Reducing unhealthy amounts of fluid in the body can lead to positive outcomes to health, including improvements in measures of fluid overload and other quality of life measures.

Demonstrated Clinical Performance

The superabsorbent material in **Fluid Manager Supplements** absorbs up to 65 times its weight in fluid.

In clinical studies, use of **Fluid Manager Supplements** resulted in clinical improvements to health.

The product provides a method for dialysis free fluid management.

In a clinical study in people with heart failure with chronic kidney disease, supplementation with **Fluid Manager Supplements** at 15 grams per day for 8 weeks resulted in a variety of clinically significant outcomes.

Improvements to health included decreases in body weight; increases in distance walked in 6-minute walk test; improvements in Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of life scores; and decreases in NYHA heart failure classification from Class III/IV to I/II.

Improvements were also demonstrated in signs of fluid overload including reductions in blood pressure, dyspnea on exertion, pulmonary rales, and peripheral edema in extremities.

Increases in fecal sodium and potassium with corresponding decreases in urinary sodium and potassium were also observed.

NON CLINICAL PERFORMANCE

Extensive non clinical studies have been performed with the superabsorbent material in **Fluid Manager**.

Observations:
The superabsorbent material is capable of absorbing fluid via the gastrointestinal route, resulting in:
- An increase in fecal volume.
- An increase in fecal water content.
- A decrease in mean urinary excretion rate.
- A decrease in average daily urine output.

Fecal volume increases while urine volume decreases as a result of use. Further, urinary output decreased even with increased water intake. This measure thus supports that the superabsorbent material removes fluid from the body that would normally have been removed by the kidneys.

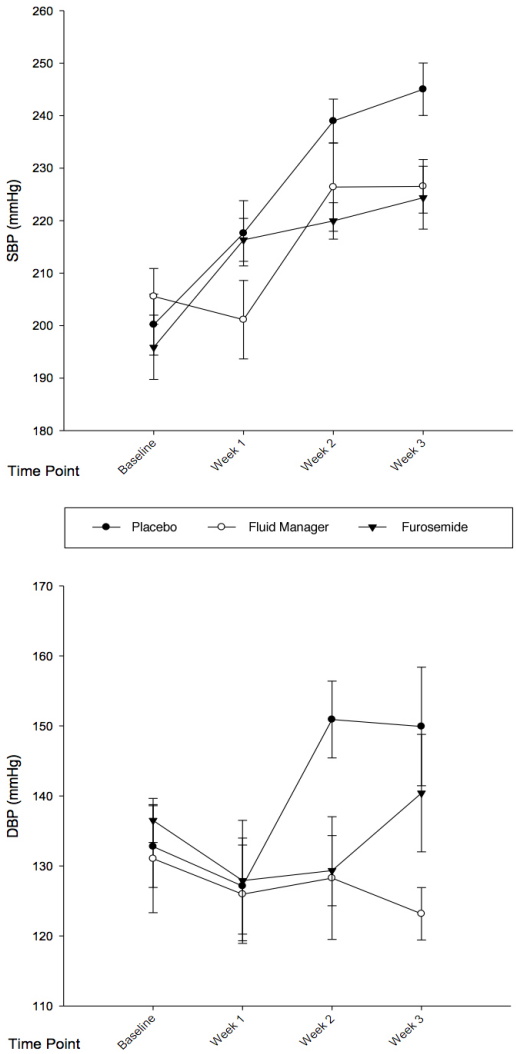
Performance data for effectiveness of **Fluid Manager** in 5/6 nephrectomized rats showed:
- Better control of fluid retention
- Absorption of water that would otherwise cause edema
- Increased survival time
- Control of serum electrolytes and uremic toxins

Dialysis free fluid management resulted in decreased the rate of rise of serum creatinine and allowed for 11 weeks extended survival time and return of BUN to normal in combination with 1/6th kidney function.

Performance data for effectiveness in a patient ESRD dog for 13 weeks showed:
- Better management of fluid than on hemodialysis alone
- Decreased rate of rise of urea
- Improvement in blood pressure

Non clinical pharmacology data demonstrated that **Fluid Manager** absorbs sodium and potassium. Non clinical safety data showed that **Fluid Manager** was not genotoxic, was not associated with adverse effects in safety studies of the central nervous system, cardiovascular, gastrointestinal, or renal systems, and was not associated with adverse effects or abnormal pathology in dogs or rats.

Fluid Manager vs. Popular Diuretic vs. Placebo



In a study conducted to determine the effects of **Fluid Manager** and furosemide on blood pressure on spontaneously hypertensive (SHR) rats. **Fluid Manager** showed control of systolic blood pressure similar to furosemide and control of diastolic blood pressure that was better than furosemide. Both were better than placebo.

Although intake of energy was the same in all groups, **Fluid Manager**-fed rats decreased their body weight by about 10 grams over three weeks while both the control group and the furosemide group gained over 40 grams.

GLP Good Laboratory Practice

Animal testing for safety and performance was conducted in compliance with the principles of Good Laboratory Practice (GLP).

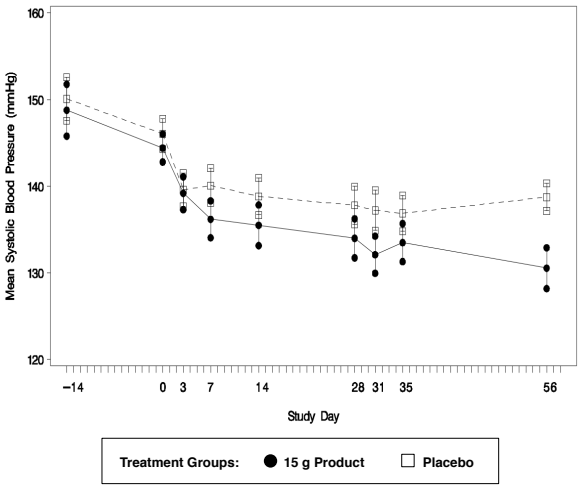
CLINICAL PERFORMANCE

Improvements across measures of fluid overload, functional capacity, and quality of life as demonstrated in clinical studies support that dialysis free fluid management has shown beneficial effects when it is used to support fluid management and control.

A double-blind, randomized, parallel, placebo-controlled clinical study examining the effect of the product in people with heart failure and chronic kidney disease was conducted and had the following performance:

Blood Pressure

Subset analyses of people with baseline systolic blood pressure >130 mmHg revealed significant differences at Week 8 between product and placebo (p=0.019, systolic and p=0.012 diastolic) when using Repeated Measures Analysis of Covariance.



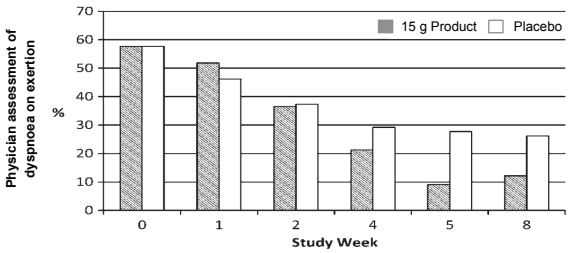
Heart Failure Detection: Changes in Neuroendocrine Markers

Frequency analysis of speople with NT-proBNP ≠1000 and >1000 pg/mL revealed a significant difference at Week 4 between product and placebo (p=0.0389) when using a chi-square test comparing proportions.

Study Visit	Variable	Product (N=59)	Placebo (N=52)	p-value
Screening	NT-proBNP ≠1000 pg/mL	0 (0.0%)	1 (1.9%)	0.2846
	NT-proBNP >1000 pg/mL	59 (100.0%)	51 (98.1%)	
End of Week 4	NT-proBNP ≠1000 pg/mL	4 (8.5%)	0 (0.0%)	0.0389
	NT-proBNP >1000 pg/mL	43 (91.5%)	48 (100.0%)	
End of Week 8	NT-proBNP ≠1000 pg/mL	5 (12.2%)	1 (2.2%)	0.0656
	NT-proBNP >1000 pg/mL	36 (87.8%)	45 (97.8%)	

Dyspnea on Exertion

The frequency of marked or disabling exertional dyspnea by physician assessment decreased over time. The percentage of people reporting moderately or markedly better breathing by the 7-point Likert scale was 21.3% in the product group at Week 4 (P=0.567), and 36.6% (P = 0.127) at Week 8.



Pulmonary Rales

A larger percentage of subjects who had pulmonary rales at Baseline had an absence of pulmonary rales at Week 8.

	Product	Placebo
Patients with pulmonary rales present at Baseline and **absent at Week 4**	26 (55.3%) (N=47)	27 (56.3%) (N=48)
Patients with peripheral edema present at Baseline and **absent at Week 8**	26 (63.4%) (N=41)	27 (58.7%) (N=46)

Improvements in NYHA Functional Classification (Heart Failure Class)

The difference in proportions of people with at least one class improvement from Baseline to Week 8 was significant in favor of the product (p=0.002)

NYHA Class	Product (N=59)	Placebo (N=52)
II	17 (41.5%)	6 (13.0%)
III	24 (58.5%)	38 (82.6%)
IV	0 (0.0%)	2 (4.3%)

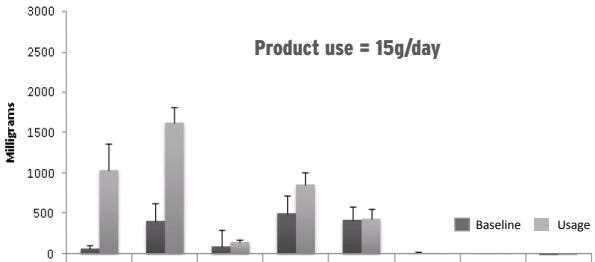
Subjects with at Least One Class Improvement from Baseline at Week 8	**20 (48.8%)**	**8 (17.4%)**

CLINICAL PERFORMANCE

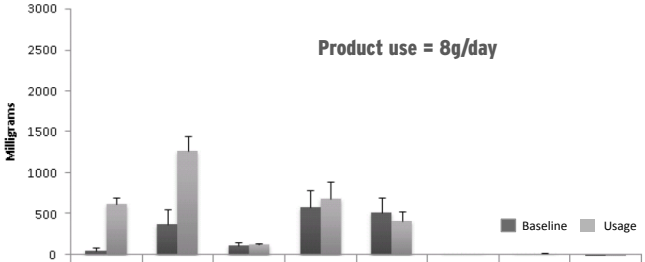
An open label, multiple dose study examining the effect of dialysis free fluid management in people with end stage renal disease (ESRD) was conducted and had the following performance:

Fecal Content and Concentration of Cations

Large increases in fecal sodium and potassium content occurred after two weeks of supplementation. Fecal content of sodium and potassium increased in a dose-dependent manner. while decreases in urinary content of sodium and potassium also occurred.



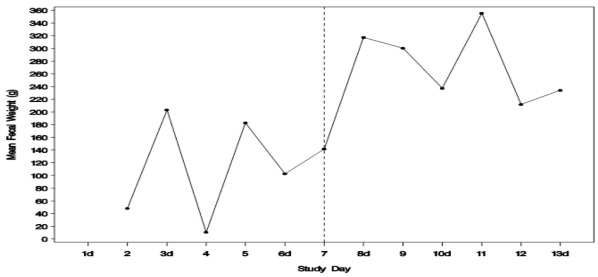
	Na	K	Mg	Ca	P	Fe	Zn	Cu
Baseline	67.189	411.596	100.642	499.135	418.255	13.939	11.045	0.886
Usage	1041.073	1626.77	150.85	861.072	435.399	12.837	13.787	0.739



	Na	K	Mg	Ca	P	Fe	Zn	Cu
Baseline	52.573	377.235	111.269	581.133	515.351	13.525	8.691	0.724
Usage	616.677	1273.769	126.346	690.217	415.954	15.083	15.149	0.587

Daily Average Fecal Weight

A mean increase from baseline in daily average fecal weight demonstrates the effectiveness of the product to absorb fluid from the body via the gastrointestinal route. Increases in fecal weight occurred within a day of supplementation.



Predialysis and Postdialysis Blood Pressure and Body Weight

In an open label, nonrandomized, multiple dose clinical study to assess the safety, tolerability, and efficacy of the product in people with ESRD who were maintained on 3-times/weekly hemodialysis, supplementation resulted in lower predialysis and postdialysis systolic and diastolic blood pressure as well as lower predialysis body weight during the supplementation period versus baseline.

Parameter	Statistic	Product use: 15 grams/day (N=5)					
		Predialysis			Postdialysis		
		Baseline Period	Supplementation Period	Change From Baseline During Usage	Baseline Period	Supplementation Period	Change From Baseline During Usage
		Days 3-6 Daily Average	Days 10-13 Daily Average		Days 3-6 Daily Average	Days 10-13 Daily Average	
Sitting Systolic Blood Pressure (mmHg)	n	5	5		5	5	5
	Mean	147.9	146.1	-1.8	141.1	129.7	-11.3
	SD	10.91	16.36	12.11	15.42	17.75	12.15
	Median	150.7	138.3	-5.7	139	125.3	-13.7
	Min, Max	132, 157	135, 174	-12, 17	123, 162	105, 148	-25, 7
Sitting Diastolic Blood Pressure (mmHg)	n	5	5	5	5	5	5
	Mean	83.5	83.3	-0.1	81.6	78	-3.6
	SD	9.85	4.71	6.98	9.72	14.94	6.89
	Median	82	86.7	-0.3	77	70.7	-5
	Min, Max	72, 97	77, 87	-10, 8	73, 94	64, 98	-10, 8
Weight (kg)	n	5	5	5	5	5	5
	Mean	91.86	90.79	-1.07	88.95	88.15	-0.79
	SD	14.253	13.662	0.855	14.055	13.431	0.735
	Median	94.17	92.5	-0.77	90.03	89.13	-0.67
	Min, Max	70.4, 107.5	70.0, 105.3	-2.2, -0.2	67.5, 104.3	67.5, 102.3	-2.0, 0.0

SAFETY AND PRECAUTIONS

Fluid Manager Supplements have been studied in healthy volunteers, end stage renal disease patients, and heart failure patients with and without chronic kidney disease. Generally, use of the product is well-tolerated.

As with anything that travels through the GI tract, there can be a risk of adverse abdominal effects, abdominal distention, or discomfort. If you experience undesirable gastrointestinal effects while taking **Fluid Manager Supplements**, discontinue use.

The product is not associated with and has not demonstrated any serious risks. Any adverse events are generally dose dependent, mild to moderate, transient, reversible, expected, and resolve without medical treatment or pharmacologic intervention.

Studies show that patients taking multiple medications at a time separated from ingesting the product had no evidence of altered drug activity or effects on drug absorption.

Fluid Manager Supplements are not intended as a replacement for hemofiltration or hemodialysis.

While the superabsorbent material in **Fluid Manager Supplements** will absorb fluid, use of the product is not for everyone and may not result in beneficial outcomes depending on the level of poor health of each individual, level of commitment to other healthy lifestyle habits, or the stage and severity of other underlying health conditions.

Recognized as Safe by Global Regulatory

The product is derived from material that is recognized as safe by global regulatory agencies.

These determinations support its safe use as a supplement that supports fluid management and control:

Inclusion in the Priority-Based Assessment of Food Additives (PAFA).

Recognized by the Codex Alimentarius Commission of the World Health Organization (WHO) as a food additive.

Not classified as hazardous by the Globally Harmonized System (GHS).

Recognized as safe, non-toxic, and non-carcinogenic by the National Toxicology Program (NTP), International Agency for Research on Cancer (IARC), and Occupational Safety and Health Administration (OSHA).

Recognized as direct and indirect food additives permitted for human consumption by the US FDA.

Included in the EU List of Authorized Food Additives and approved for use in food supplements. (EU 2023/440)

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