PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Multiforce®
Alkaline Powder

COMPLEMENTARY MEDICINE

Combination Product

This unregistered medicine has not been evaluated by the South African Health Products Regulatory Authority for its quality, safety or intended use.

SCHEDULING STATUS

S0

1 NAME OF THE MEDICINE

A.VOGEL MULTIFORCE® ALKALINE POWDER

Combination Product

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each 7,5 g powder contains:

Calcium citrate tetrahydrate	..... 145 mg
Calcium phosphate, dibasic	..... 974 mg
Dimagnesium phosphate trihydrate	..... 244 mg
Magnesium citrate	..... 315 mg
Potassium bicarbonate	..... 783 mg
Potassium citrate monohydrate	..... 870 mg
Providing elemental:	
Calcium	..... 254 mg
Magnesium	..... 59 mg
Phosphorus	..... 219 mg
Potassium	..... 619 mg
Homeopathic proprietary blend Urtica/A.Vogel Urticalcin	..... 1000 mg
Providing:	
Urtica dioica L. (*Urtica dioica*) and/or *Urtica urens* L. (*Urtica urens*)	D1
Silicon dioxide (Silicea)	D6
Calcium hydrogen phosphate dihydrate (*Calcarea phosphorica*)	D6
Disodium phosphate dodecahydrate (*Natrum phosphoricum*)	D6
Ostrea edulis L. (*Calcarea carbonica*)	D4
Malpighia glabra (Acerola) [Fruit]	..... 100 mg
Providing: vitamin C botanical extract	..... 5 mg

Contains sugar:

Lactose	..... not more than 980 mg
Maltodextrin	..... not more than 50 mg
Mannitol	..... 3 069 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to off-white, pinkish, fine, free-flowing powder containing fine black particles (organic material from the homeopathic blend) with a sweetish odour and a slightly acidic or bitter taste.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A.VOGEL MULTIFORCE® ALKALINE POWDER is a source of calcium, magnesium, phosphorus and potassium, as well as citrate and bicarbonate salts (alkalising minerals) and has a systemic alkalising effect.

A.VOGEL MULTIFORCE® ALKALINE POWDER is a multi-mineral combination product, containing health supplements (minerals) and a homeopathic complex that supports the body's acid buffering mechanism by providing essential alkaline minerals required to combat a typical acidogenic diet (high in animal protein and low/deficient in fruit, vegetables and minerals) and lifestyle, thereby assisting in addressing the negative consequences thereof.

4.2 Posology and method of administration

Posology

Adults:

Take 1 sachet or 1 heaped teaspoon (approx. 7,5 g) once daily.

Special populations

Elderly population:

No dosage adjustment is required for this population. Refer to section 4.4.

Paediatric population

This product is not indicated for patients younger than 18 years.

Method of administration

For oral use only.
Dissolve in a large glass of water and stir well before drinking.
Take on an empty stomach.

4.3 Contraindications

- A.VOGEL MULTIFORCE® ALKALINE POWDER should not be used in patients who have a hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

- Do not discontinue the use of prescribed medication without consulting a healthcare professional.
- Consult a healthcare professional and/or use under medical supervision in:
  - Patients on calcium and/or potassium restricted diets.
  - Patients with moderate to severely compromised renal function.
  - Patients with uncontrolled or unstable diabetes.

Lactose / maltodextrin warning:

- A.VOGEL MULTIFORCE® ALKALINE POWDER contains lactose and maltodextrin which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take A.VOGEL MULTIFORCE® ALKALINE POWDER.

4.5 Interaction with other medicines and other forms of interaction

Refer to section 4.4.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

No information available.

Pregnancy

The safety of this product during pregnancy has not been established. During pregnancy A.VOGEL MULTIFORCE® ALKALINE POWDER should be taken under the supervision of a medical practitioner.

Breastfeeding

The safety of this product during lactation has not been established. During breastfeeding A.VOGEL MULTIFORCE® ALKALINE POWDER should be taken under the supervision of a medical practitioner.

Fertility

Fertility studies have not been performed.
No effect on fertility expected.

4.7 Effects on ability to drive and use machines

A.VOGEL MULTIFORCE® ALKALINE POWDER has no or negligible influence on mental and/or physical ability to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

Gastro-intestinal side effects that occur more frequently include:

- flatulence
- diarrhoea

In case of allergic or sensitivity reactions, discontinue use of product and consult your healthcare professional immediately.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

None known.
With excessive use, symptoms of alkalosis may occur.
Treatment of overdosage should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

D33.7 Combination Product

A.VOGEL MULTIFORCE® ALKALINE POWDER is a multi-mineral dietary supplement consisting of calcium (phosphate and citrate), magnesium (phosphate and citrate) and potassium (citrate and bicarbonate). Such minerals support the body's acid buffering mechanism by complementing compensatory mechanisms which combat high acid load from a typical acidogenic diet (high in animal protein and deficient in fruit and vegetables).

By assisting the body's acid buffering mechanisms A.VOGEL MULTIFORCE® ALKALINE POWDER may assist with the following conditions, which are associated with an acidogenic diet and chronic sub-clinical systemic metabolic acidosis (CSSMA):

Decreased bone mineral density

A large body of evidence supports the adverse effects of CSSMA on bone metabolism, suggesting it as a primary risk factor for bone health with Fenton *et al*. (2008) estimating that the amount of calcium lost as a result of the modern acidogenic diet to be as high as 480 g over 20 years, i.e. approximately half the total skeletal calcium mass.

The documented effects of CSSMA on bone metabolism include:

- Osteoblast activity decreased (Bushinsky *et al*. 2003; Frick & Brushinsky, 2010).
- Osteoclast activity increased (Bushinsky *et al*. 2003; Frick & Brushinsky, 2010; Yan *et al*. 2016).
- Promotion of bone resorption (Yan *et al*. 2016; Buclin *et al*. 2001).
- Decreased gene expression of bone matrix proteins (Bushinsky *et al*. 2003; Frick & Brushinsky, 2010).
- Decreased alkaline phosphatase activity (Bushinsky *et al*. 2003; Frick & Brushinsky, 2010).
- Increased urinary calcium excretion (Jajoo *et al*. 2006).
- Increased parathyroid hormone (PTH) levels (associated with net acid excretion (NAE)) (Jajoo *et al*. 2006).
- Increased N-telopeptide (associated with NAE) – a marker of bone resorption (Jajoo *et al*. 2006).

Association between the acidogenic diet and reduction in bone mineral density is also well documented; according to Buclin *et al*. (2001) an acidogenic diet consumed for 4 days led to a 74% increase in urine calcium excretion and 19% increase in the bone resorption marker N-telopeptide compared to an alkaline diet. A study of 1056 women confirmed a positive association between high Net Endogenous Acid Production (NEAP) values and lower femur bone mineral density and reduced hip and spine bone mass (New *et al*. 2004). Conversely, a low Potential Renal Acid Load (PRAL) (alkaline) diet has been shown to reduce bone turnover in postmenopausal women i.e. a diet with PRAL -23 mEq/day consisting of more than 9 servings of fruit and vegetables per day for 12 weeks resulted in a reduction in urine calcium excretion, increased urine pH and had a favourable influence on bone turnover markers i.e. reduction in procollagen type I N propeptide (P1NP) and C-terminal telopeptide of type I collagen (CTX) (Gunn *et al*. 2015).

An association between dietary alkalising agents (potassium, magnesium and fruit and vegetable intake) was made with both basal bone mineral density (BMD) and 4-year longitudinal change in BMD in elderly subjects confirming the ability of alkalising dietary interventions to contribute to the maintenance of BMD (Tucker *et al*. 1999). In addition, a meta-analysis of 25 studies exploring the association between calcium excretion and net acid excretion by Fenton *et al*. (2008) also confirmed the linear association between these variables, i.e. increased calcium excretion occurring as a result of an acidogenic diet.

Potassium citrate supplementation significantly increased bone mass and reduced urinary calcium excretion in a 12 month, controlled, double-blind trial of 161 osteopenic, postmenopausal women (Jehle *et al*. 2006). Similarly, supplementation with potassium citrate attenuated the negative effect of a high salt diet on urinary calcium loss and reduced elevation of bone resorption marker N-telopeptide in 60 postmenopausal women in a randomised, placebo-controlled trial (Sellmeyer *et al*. 2002). Potassium citrate supplementation in postmenopausal women with low bone density also resulted in a significant decrease in net acid excretion, urinary deoxypyridinolines, hydroxyproline-to-creatinine ratios and serum osteocalcin suggesting that supplementation with alkaline salts such as potassium citrate can reduce bone resorption by countering the effects of chronic acidaemia from protein-rich diets (Marangella *et al*. 2004).

Potassium bicarbonate supplementation similarly resulted in a significant reduction in urine calcium excretion in a dose-dependent manner compared with placebo in postmenopausal women (Frassetto, *et al*. 2005). In another trial, potassium bicarbonate supplementation resulted in significantly reduced urinary calcium, phosphorus and hydroxyproline excretion and increased serum osteocalcin concentrations. Researchers reported that by neutralising endogenous acid potassium bicarbonate improved calcium and phosphorus balance, reduced bone resorption and increased the rate of bone formation (Sebastian *et al*. 1994). This action was re-confirmed by Dawson-Hughes *et al*. (2009) who concluded that potassium bicarbonate supplementation leads to significant reductions in urinary N-telopeptide and calcium excretion attributing the favourable effect on bone resorption and calcium excretion to bicarbonate supplementation and concluding that increasing alkali content of the diet may attenuate bone loss in healthy older adults.

Joint pain and reduced mobility and flexibility

Collins *et al*. (2013) discovered acidosis to be a factor which negatively affects human osteoarthritic chondrocytes by increasing cellular reactive oxygen species (ROS) and reducing mitochondrial membrane potential and cellular antioxidants. Synovial fluid acidosis was also shown to correlate with features of radiological joint destruction and granulocyte concentration in knee rheumatoid arthritis ($p<0,002$) (Geborek *et al*. 1989) with acidosis being a feature of chronic inflammatory arthritis.

82 Patients with chronic low back pain received a lactose based alkaline multimineral supplement over a 4 week period resulting in a significant reduction (49%) in mean ARS (Arhus Low Back Pain Rating Scale) scores, blood buffering capacity increased significantly as did blood pH and intracellular magnesium (Vormann, *et al*. 2001). Researchers concluded that disturbed acid-base balance may contribute to symptoms of low back pain. Intracellular magnesium is necessary for enzyme systems and the activation of vitamin D which too improves back pain.

Kidney stones

As a result of the compensatory response to CSSMA, urinary excretion of calcium and oxalate salts increases (Carnuba *et al*. 2017; Adeva *et al*. 2011) and citrate excretion decreases (Trinchieri *et al*. 2006). The lack of urinary citrate is particularly problematic in this context because when it is sufficiently present in urine, it serves to inhibit the formation and agglomeration of calcium oxalate crystals (Adeva *et al*. 2011; Trinchieri *et al*. 2006). Lower levels of urinary citrate in the presence of higher calcium and oxalate due to CSSMA thus increases the risk of stone formation.

A systematic review and meta-analysis including 4 trials and 374 participants concluded that potassium citrate supplementation significantly protected against recurrence of nephrolithiasis during the year after extracorporeal shock wave lithotripsy (Carvalho *et al*. 2017). Similarly, a Cochrane review of seven trials including 477 participants concluded that citrate salts significantly reduce kidney stone size and prevent stone formation as well as reduce the need for retreatment or stone removal (Phillips *et al*. 2015). Frassetto & Kholstadt (2011) also confirm that in order to prevent calcium oxalate, cystine and uric acid stones, urine should be alkalinised by eating a diet high in fruits and vegetables, taking supplemental or prescription citrate (calcium, magnesium or potassium citrate) or drinking alkaline mineral waters. For calcium oxalate stones these authors specifically suggest calcium citrate, magnesium citrate and potassium citrate supplementation (Frassetto & Kholstadt 2011). Various other trials confirm the benefit of potassium citrate supplementation accordingly (McNally *et al*. 2009; Soygur *et al*. 2002) including a paediatric trial in patients following a therapeutic ketogenic diet (McNally *et al*. 2009).

Worsening of symptoms of osteoarthritis, such as pain and stiffness.

One hundred patients with osteoarthritis (OA) of the hands (47 – 89 yrs.) were given one heaped teaspoon (7,5 g) of A.VOGEL MULTIFORCE® ALKALINE POWDER twice daily in a randomised, placebo-controlled, cross-over trial for a period of 28 days. Significantly less pain, tenderness and stiffness of the hand joints was achieved within 2 weeks of treatment and the majority were able to successfully stop their pain killers. The mode of action being a systemic alkalising effect confirmed by parallel, sustained increases in urinary pH, urine pH specifically reflecting dietary acid-base load and more alkaline urine being specifically associated with an alkaline diet (van Velden *et al*. 2015).

Pain and discomfort of the digestive tract due to excess acid

Chronic metabolic acidosis which occurs when excessive endogenous acid is produced or when organs such as the lungs, kidneys, liver and gastrointestinal tract responsible for the regulation and elimination thereof are compromised and/or when the bicarbonate buffer system is compromised has a negative impact on liver and pancreatic function (Melamed & Melamed 2014).

Both these digestive organs produce alkaline substances namely bile and pancreatic juice containing high levels of bicarbonate. Systemically lowering pH negatively influences the action of pancreatic juice leading to indigestion. Dysbiosis also results as a consequence of acidification of pancreatic juice as, when more acidic, its antimicrobial action is compromised. Pancreatitis may also result when pancreatic juice is acidified as the proteases within are prematurely activated whilst still within the pancreas. Similarly, acidification of bile leads to precipitation of bile acids irritation the biliary tract and possibly leading to stone formation (Melamed & Melamed 2014). A combination of both altered bile and pancreatic juice pH may stimulate disordered contractions within the duodenum and bile reflux. Regulating and restoring acid-base balance may be a useful intervention for various gastrointestinal disorders and sufficient evidence exists confirming that restoring bicarbonate buffering activity in the blood can result in improved digestion (Melamed & Melamed 2014).

In addition to systemic alkalising action, A.VOGEL MULTIFORCE® ALKALINE POWDER contains potassium bicarbonate, which is used in medicine as an antacid in the stomach; used to neutralise gastric acid. It is generally regarded as a suitable, safe and effective ingredient for over-the-counter antacids. A.VOGEL MULTIFORCE® ALKALINE POWDER also contains the antacid calcium phosphate.

Compromised physical performance, fatigue, and delayed recovery post-exercise
According to Hawley and Reilly (1997), fatigue is associated with a more acid environment which may negatively impact on exercise performance in terms of rating of perceived exertion and reduced force production. Research confirms that intense exercise induces a state of metabolic acidosis resulting in increased demand on the body's buffering mechanisms leading to disturbance in mineral balance and resulting in increased calcium excretion in the urine (Berardi *et al*. 2008; Cardinale *et al*. 2007; Ashizawa *et al*. 1998). Athletes are also known to follow higher protein diets which further increases urine acidity and calcium loss in the urine (Berardi *et al*. 2008; Cardinale *et al*. 2007). Research has also confirmed that the pre-exercise systemic pH and blood pH buffering capacity impacts significantly on recovery kinetics and endurance capacity in recurrent exercise (Berardi *et al*. 2008; Robergs *et al*. 2005). Low-grade metabolic acidosis caused by diet may compound the additional acidogenic burden induced by exercise which may compromise performance and recovery time (Berardi *et al*. 2008). Alkalising supplements, by buffering additional acidity during high-intensity exercise, may delay the onset of fatigue. This has been confirmed most specifically in high intensity exercise involving larger muscle movement and faster motor unit recruitment (Seebohar 2011; Requena *et al*. 2005).

Increased uric acid levels and episodes of gout
It has been determined that gout sufferers often have low urine pH (Takahashi *et al*. 2007; Pakpoy 1965) which is also a major risk factor for the development of uric acid stones (Alvarez-Nemegyei *et al*. 2005; Abate *et al*. 2004).

Both a preliminary trial and a subsequent cross-over trial confirmed that an alkaline diet facilitates the elimination of uric acid via urine. In the second cross-over trial aimed to determine the influence of an acidic diet (high in protein and low in fruit and vegetables) or an alkaline diet (low in protein and high vegetable and fruit) on uric acid levels, urine pH and uric acid excretion. Significant differences were observed for both serum and urine uric acid levels between the acidic and alkaline diet interventions. An acidic diet resulted in significantly higher serum uric acid and significantly lower urine uric acid and low pH compared with the alkaline diet i.e. uric acid may be reabsorbed from acidic urine and less so from alkaline urine. The researchers concluded that an alkaline diet and subsequent higher urine pH thus facilitates the excretion of uric acid via urine (Kanbara *et al*. 2010).

A systematic review reported that there is evidence (limited) that urine alkalisation with potassium citrate may be an effective and safe intervention in uric acid nephrolithiasis (Teixeira *et al*. 2013). Ferrari and Bonny (2004) report that the most important risk factor for the development of uric acid stones is low urine pH (less than 5,5 pH) as opposed to increased uric acid excretion and recommend increasing urine pH to pH 6,2 and 6,8 as a therapeutic intervention with potassium citrate (or sodium bicarbonate) which is also an effective method of dissolution of existing stones with potassium citrate being the treatment of choice in preventing recurrence.

5.2 Pharmacokinetic properties
No information on this formulation available.
The pharmacokinetic data of the single ingredients are well known and described in the literature.

5.3 Preclinical safety data
No data available on the formulation.
The pre-clinical data of the single ingredients are well known and described in the literature.

Clinical studies:
The systemic alkalising effect of A.VOGEL MULTIFORCE® ALKALINE POWDER was confirmed in a double-blind, placebo-controlled cross-over trial in which a sustained increased in urinary pH was achieved, urine pH specifically reflecting dietary acid-base load and more alkaline urine being specifically associated with an alkaline diet (van Velden *et al*. 2015).

One hundred patients with OA of the hands (47 – 89 yrs.) were given one heaped teaspoon (7,5 g) of A.VOGEL MULTIFORCE® ALKALINE POWDER twice daily in a randomised, placebo-controlled, cross-over trial for a period of 28 days (van Velden *et al*. 2015). Significantly less pain, tenderness and stiffness of the hand joints was achieved within 2 weeks of treatment and the majority were able to successfully stop their pain killers. The mode of action being a systemic alkalising effect confirmed by parallel, sustained increases in urinary pH, urine pH specifically reflecting dietary acid-base load (Welch *et al*. 2008) and more alkaline urine being specifically associated with an alkaline diet.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol

Contains sugar:

Lactose	..... not more than 980 mg
Maltodextrin	..... not more than 50 mg
Mannitol	..... 3 069 mg

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at or below 25 °C in a cool, dry place.
Protect from light and moisture.
Store in the original package / container.
Keep container tightly closed.

6.5 Nature and contents of container
Packed in a HDPE plastic container with a tamper evident seal and a plastic screw cap.
Sachets packed in an outer carton.

Pack sizes:
105 g, 225 g and 450 g containers.
Individual 7,5 g sachets in packs of 10's and 30's.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product
No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION
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8 REGISTRATION NUMBER(S)/REFERENCE NUMBER
Listing number: 000012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
To be allocated.

10 DATE OF REVISION OF TEXT
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