STD Pharmaceutical

kreussler PHARMA

Comprehensive Leg Treatment with Aethoxysklerol® and Fibrovein®

Sclerotherapy from small to large varicose veins

Sclerotherapy with Combined Forces

New Strategic Partnership of Kreussler Pharma and S.T.D. Pharmaceuticals

At the end of 2023, Kreussler and S.T.D. Pharmaceuticals announced their new alliance to further solidify the worldwide importance of sclerotherapy as an indispensable technique for treating varicose veins. With this partnership the two most widely recognised sclerosing agents are made available to doctors with combined forces to guarantee treatment of the smallest to large varicose veins and optimal care for patients with varicose veins.

Complete Leg Treatment Needs Sclerotherapy

Recent epidemiologic studies confirm the growing importance of varicose vein disease in an ever-aging population. One of the most established treatment options for varicose veins is sclerotherapy, which offers the unique advantage that all types of varicose veins can be treated successfully.

- According to the European guidelines (Rabe et al., 2014), all types of varicose veins can be effectively treated with sclerotherapy
- Sclerotherapy is gold standard for the treatment of C1 varicose veins
- In clinical practice, sclerotherapy is the most used treatment for incompetent perforating veins
- Sclerotherapy is the treatment of choice for tortuous varicose veins and a very good treatment method for recurrent varicose veins after surgical or thermal failure
- Sclerotherapy is a good and minimally invasive alternative to phlebectomy in the treatment of tributary and accessory varicose veins
- For patients with active venous leg ulceration, ablation of the sub-ulcer venous plexus using ultrasound guided foam sclerotherapy should be considered as part of the treatment strategy
- For complete leg treatment, sclerotherapy is indispensable as adjunct to thermal and surgical methods for truncal vein treatment
- Foam sclerotherapy for truncal veins is a cost-effective and patient-friendly non-thermal alternative, especially for older, multimorbid and obese patients and where it is not possible to pass a thermal catheter along the length of the vein

Available Concentrations

(Differ from country to country)

mg/ml	%	Product
2.5 mg/ml	0.25%	Aethoxysklerol®
5 mg/ml	0.5%	Aethoxysklerol®, Fibrovein®
10 mg/ml	1%	Aethoxysklerol®, Fibrovein®
20 mg/ml	2%	Aethoxysklerol®
30 mg/ml	3%	Aethoxysklerol®, Fibrovein®

Comparison of Properties of STS and POL

Properties	Sodium tetradecyl sulfate (STS)	Polidocanol (POL)
Molecule	$C_{14}H_{29}NaSO_4$	$C_{12}H_{25}(OCH_2CH_2)_nOH$ n=9
INN	Sodium tetradecyl sulfate	Lauromacrogol 400
Sclerosing agent class	Anionic detergent	Non-ionic detergent
Local anaesthetic effect	No	Yes
Mechanism of action	Endothelial damage (destroys cell membranes), injury to media stronger than with POL	Endothelial damage (destroys cell membranes), is more forgiving than STS (Duffy, 2010)
Potency on cells (Kobayashi et al. 2006, Bush and Bush 2017)	The same concentration of liquid STS is in cell experiments 2 times more potent than liquid POL	
Median endothelial cell loss at 15 minutes in harvested GSVs with 3% foam (McAree et al., 2012)	98%	86%
Foam viscosity (Wong et al., 2015)	Viscosity does not increase at higher concentrations	Viscosity increases at higher concentrations
Preservatives	Benzyl alcohol (20 mg/ml)	None
Ethanol 96%	None	5% (v/v)
Incompatibilities (SmPC)	Should not be mixed with other medicines, e.g., heparin	When combined with other anaesthetics, there is a risk of an additive effect on the cardiovascular system
Storage (SmPC)	No special storage conditions. Do not freeze. Keep the ampoules protected from light.	No special storage precautions. Do not freeze.

Recommendations for the use of Fibrovein® and Aethoxysklerol®

Use one agent per session (interactions unknown)!

Use POL

- For aesthetic treatments
- Also recommended for beginners of sclerotherapy
- For patients allergic to STS

Use STS

- For large diameter varicose veins, especially for great saphenous veins
- If treatment with POL was not effective
- For patients allergic to POL

From Small to Large Varicose Veins – Choose the Optimal Concentration

Large varicose veins (deeper below the fascia) and surgical recurrence in the groin

Fibrovein®	3% foam
Aethoxysklerol®	2%, 3% foam

Small and medium varicose veins

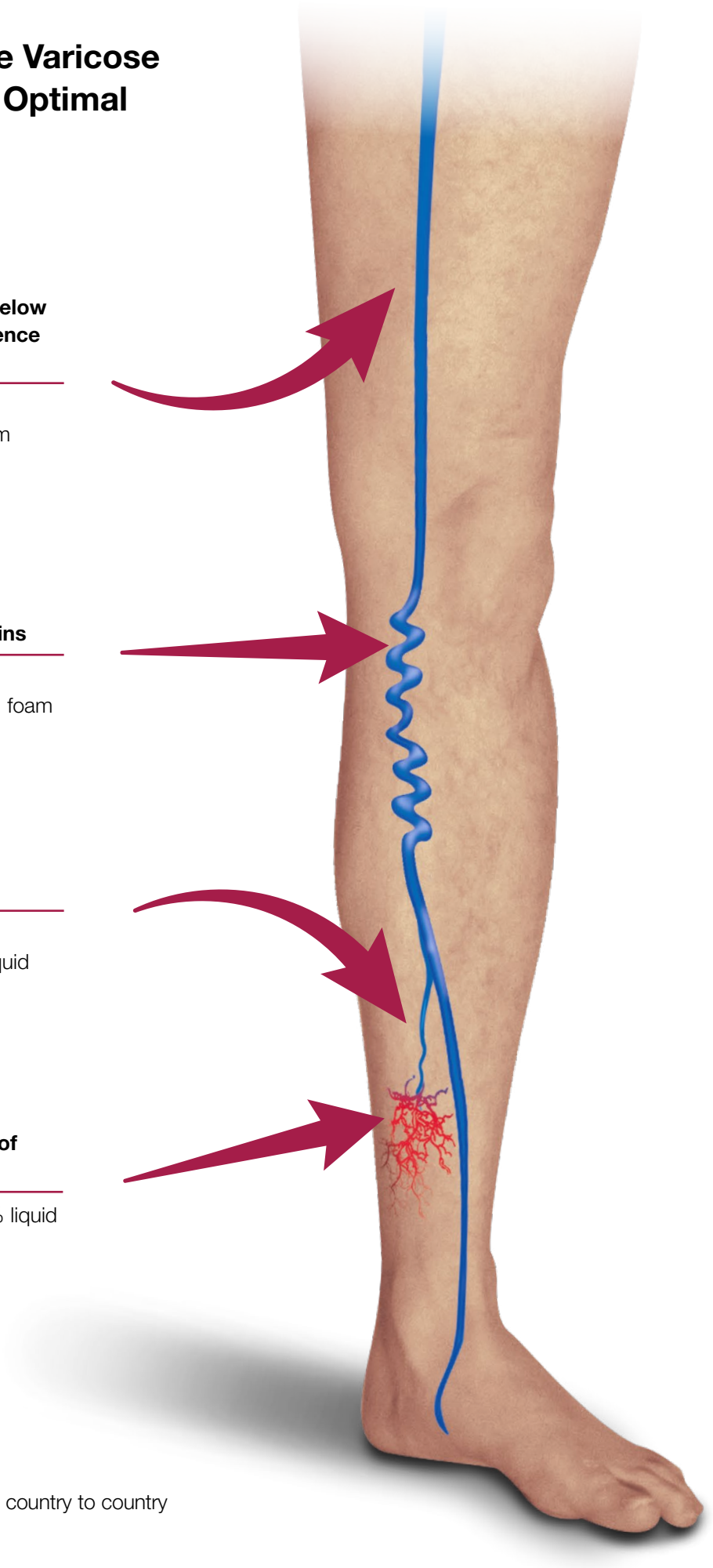
Fibrovein®	1% foam
Aethoxysklerol®	1%, 2%, 3% foam

Reticular veins

Fibrovein®	0.5% liquid
Aethoxysklerol®	0.5%, 1% liquid

Spider veins and central veins of spider veins

Aethoxysklerol®	0.25%, 0.5% liquid



Available concentrations differ from country to country

Comparative Strengths and Indications According to the European Guidelines (Rabe et al., 2014)

Sclerotherapy is still the gold standard for treating reticular varicose veins and telangiectasias with a success rate of up to 95%.

Suggested STS and POL concentrations in liquid sclerotherapy

	% STS	% POL
Telangiectasias	0.1 – 0.2	0.25 – 0.5
Reticular varicose veins	0.5	0.5 – 1
Small varicose veins	1	1

Foam has been shown in numerous clinical studies to be at least twice as effective as liquid and is therefore mainly used for C2 to C6 varices, i.e., for larger varicose veins.

Suggested STS and POL concentrations in foam sclerotherapy

	% STS	% POL
Tributary varicose veins	Up to 1	Up to 2
Saphenous veins < 4 mm 4 – 8 mm > 8 mm	 Up to 1 1 – 3 3	 Up to 1 1 – 3 3
Incompetent perforating veins	1 – 3	1 – 3
Recurrent varicose veins	1 – 3	1 – 3

Training for Sclerotherapy

It is a generally accepted fact that the sclerotherapy technique is essential for optimal treatment success and for obtaining results comparable with endothermal and surgical methods.

You can learn or refresh sclerotherapy at any time through sclerotherapy workshops. The training includes a comprehensive theoretical overview of sclerotherapy and live demonstrations on several patients.

You can find information at

www.aethoxysklerol-international.com
www.kreussler-pharma.de/unternehmen/termine-phlebologie
www.fibrovein.co.uk/videos
www.fibrovein.co.uk/workshop

References

Rabe E et al. European guidelines for sclerotherapy in chronic venous disorders. Phlebology. 2014, 29(6):338-54

Duffy DM Sclerosants: A comparative review. Dermatol Surg. 2010, 36 Suppl 2:1010-25

Kobayashi S et al. Dose- and time-dependent liquid sclerosant effects on endothelial cell death. Dermatol Surg. 2006, 32:1444-1452

Bush R and Bush P Evaluation of sodium tetradecyl sulfate and polidocanol as sclerosants for leg telangiectasia based on histological evaluation with clinical correlation. Phlebology. 2017, 32:496-500

McAree B et al. Comparative stability of sodium tetradecyl sulphate (STD) and polidocanol foam: impact on vein damage in an in-vitro model. Eur J Vasc Endovasc Surg. 2012, 43:721-725

Wong K et al. Basic physiochemical and rheological properties of detergent sclerosants. Phlebology. 2015, 30:339-349

Aethoxysklerol® Prescribing Information

1 Company of the pharmaceutical entrepreneur and registered office

Chemische Fabrik Kreussler & Co. GmbH, 65203 Wiesbaden, Germany

2 Name of the medicinal products and active ingredient

Aethoxysklerol 0.25%, Aethoxysklerol 0.5%, Aethoxysklerol 1%, Aethoxysklerol 2%, Aethoxysklerol 3%

Active ingredient: Lauromacrogol 400

3 Composition

1 ampoule with 2 ml contains the following amount of active ingredient:

Aethoxysklerol	Lauromacrogol 400
0.25%	5 mg
0.5%	10 mg
1%	20 mg
2%	40 mg
3%	60 mg

Other ingredients: Ethanol 96%, potassium dihydrogen phosphate, disodium phosphate dihydrate (Ph. Eur.), water for injections

4 Indications

Different concentrations of Aethoxysklerol are required, depending on the size of the varices to be treated. The following gradations of indications are applicable:

Spider veins: Aethoxysklerol 0.25% and 0.5%; only liquid

Central veins of spider veins: Aethoxysklerol 0.25%, 0.5% and 1%; only liquid

Reticular varices: Aethoxysklerol 1%; only liquid

Small varices: Aethoxysklerol 1%; liquid or foam

Medium-sized varices: Aethoxysklerol 2% and 3%; liquid or foam

Large varices: Aethoxysklerol 3%; liquid or foam

If several concentrations are stated for treatment, the diameter of the vein and the patient's individual situation should be considered. In case of doubt, the lower concentration should be chosen.

For the treatment of haemorrhoidal disease, Aethoxysklerol 3% is used but this indication is not subject to this information.

5 Contraindications

Sclerotherapy of varices is absolutely contraindicated in:

- known allergy to lauromacrogol 400 or any of the other ingredients of Aethoxysklerol
- acute severe systemic diseases (especially if untreated)
- immobility
- severe arterial occlusive disease (Fontaine stage III and IV)
- thromboembolic diseases
- high risk of thrombosis (e.g., known hereditary thrombophilia or patients with multiple risk factors such as use of hormonal contraceptives or hormone replacement therapy, obesity, smoking and extended periods of immobility)

Moreover, the following absolute contraindication applies to foam sclerotherapy:

- known symptomatic patent foramen ovale

Sclerotherapy of varices is relatively contraindicated in:

- febrile states
- bronchial asthma or known strong predisposition to allergies
- very poor general health
- arterial occlusive disease (Fontaine stage II) when treating spider veins
- leg oedema (if it cannot be influenced by compression)
- inflammatory skin disease in the area of treatment
- symptoms of microangiopathy or neuropathy
- reduced mobility

Moreover, the following relative contraindications apply to foam sclerotherapy:

- known asymptomatic patent foramen ovale
- visual, psychic or neurological symptoms after previous foam sclerotherapy

6 Adverse drug reactions

Local adverse reactions (e.g., necroses), especially of the skin and of the underlying tissue (and, in rare cases, of the nerves) were observed when treating varicose veins in the leg after inadvertent injection into the surrounding tissue (paravascular injection). The risk increases with increasing Aethoxysklerol concentrations and volumes.

In addition, the following adverse reactions were observed with the frequencies seen below:

Very common (≥ 10%); common (≥ 1% – < 10%); uncommon (≥ 0.1% – < 1%); rare (≥ 0.01% – < 0.1%); very rare, including isolated cases (< 0.01%)

Immune system disorders
Very rare: anaphylactic shock, angioedema, urticaria (generalised), asthma (asthmatic attack)

Nervous system disorders
Very rare: cerebrovascular accident, headache, migraine (with 'rare' frequency when using sclerosing foam), paraesthesia (local), loss of consciousness, confusional state, dizziness, aphasia, ataxia, hemiparesis, hypoaesthesia oral

Eye disorders
Very rare: ('rare' when using sclerosing foam) visual impairment (reversible visual disturbance)

Cardiac disorders
Very rare: cardiac arrest, stress cardiomyopathy, palpitations, heart rate abnormal

Vascular disorders
Common: neovascularisation, haematoma
Uncommon: thrombophlebitis superficial, phlebitis
Rare: deep vein thrombosis (possibly due to the underlying disease)
Very rare: pulmonary embolism, syncope (vasovagal), circulatory collapse, vasculitis

Respiratory, thoracic and mediastinal disorders
Very rare: dyspnoea, chest discomfort (sensation of pressure in the chest), cough

Gastrointestinal disorders
Very rare: dysgeusia, nausea, vomiting

Skin and subcutaneous tissue disorders
Common: skin hyperpigmentation, ecchymosis
Uncommon: dermatitis allergic, urticaria contact, skin reaction, erythema
Very rare: hypertrichosis (in the area of sclerotherapy)

Musculoskeletal, connective tissue and bone disorders
Rare: pain in extremity

General disorders and administration site conditions
Common: injection site pain (short-term), injection site thrombosis (local intravaricose blood clots)
Uncommon: necrosis, induration, swelling
Very rare: pyrexia, hot flush, asthenia, malaise

Investigations
Very rare: blood pressure abnormal

Injury, poisoning and procedural complications
Uncommon: nerve injury

7 Warnings

All Aethoxysklerol preparations contain 5% (v/v) alcohol. This must be taken into consideration in patients with previous alcoholism, pregnant women, nursing mothers and patients at increased risk (liver disease, epilepsy).

Aethoxysklerol products contain potassium, but less than 1 mmol (39 mg) potassium per ampoule.

Aethoxysklerol products contain sodium, but less than 1 mmol (23 mg) sodium per ampoule.

Sclerosants must never be injected intraarterially because this can cause severe necroses which may necessitate amputation. A vascular surgeon must be called in immediately if any such incidents occur!

An indication in the facial area must be strictly evaluated for all sclerosants because intravascular injection can lead to pressure reversal in the arteries and hence to irreversible visual disturbances (blindness).

In certain body regions such as in the foot or malleolar region, the risk of inadvertent intraarterial injection may be increased. Therefore, only small amounts should be used in low concentrations with particular care during treatment.

The recommended mean volume of sclerosing foam per session is 2 to 8 ml; the maximum volume of sclerosing foam per session (for one or more injections) is 10 ml.

When treating truncal veins, the foam injection is given at a minimum distance of 8 to 10 cm to the saphenofemoral junction. If ultrasound monitoring reveals a foam bolus in the deep vein system, muscle activation, such as dorsal flexion of the ankle joint, should be performed by the patient.

8 Classification for supply

Prescription only

9 Date of issue

February 2024

Pack size: Package with 5 ampoules

Fibrovein® Prescribing Information

Name of Product
FIBROVEIN® 3%, 1%, 0.5%

Presentation
Fibrovein is a sterile aqueous solution of sodium tetradecyl sulfate available in three strengths 3%, 1% and 0.5% each containing 2% benzyl alcohol and buffered to pH 7.6.

1 Indications

For the treatment of uncomplicated primary varicose veins, recurrent or residual varicose veins following surgery and reticular veins of the lower extremities that show simple dilation. Fibrovein is indicated in adults.

Dosage and Administration
Adults and the elderly, not indicated for children. Fibrovein is for intravenous use only. The strength of solution required depends on the size and degree of varicosity. Reticular veins should only be treated with the 0.5%, the 1% solution will be found most useful for small to medium varicosities and the 3% solution for larger varicosities.

The sclerosant should be administered intravenously in small aliquots at multiple sites along the vein to be treated either as a liquid or as a sclerosant/air mixture (foam), for the treatment of larger veins with the 1% and 3%. The objective is to achieve optimal destruction of the vessel wall with the minimum concentration of sclerosant necessary for a clinical result. If the concentration is too high necrosis or other adverse sequelae may occur.

Fibrovein 3%
Liquid: 0.5 – 2 ml each site max 4 ml
Foam: 0.5 – 2 ml each site max 16 ml

Fibrovein 1%
Liquid: 0.1 – 1 ml each site max 10 ml
Foam: 0.5 – 2 ml each site max 16 ml

Fibrovein 0.5%
Liquid: 0.1 – 1 ml each site max 10 ml

Side Effects
The most commonly reported side effects are pain on injection, urticaria, superficial thrombophlebitis and temporary skin pigmentation after treatment. Very rarely a permanent discoloration may remain along the path of the sclerosed vein segment. Ulceration may occur following extravasation of the drug. It is important to use the lowest strength that will sclerose the vein as many of the common side effects are caused by using a concentration that is too high.

Serious side effects (very rare) include intraarterial injection resulting in significant tissue necrosis including loss of the extremity, anaphylactic shock and pulmonary embolism.

Stroke like symptoms have been reported. Prescribers should consult the Summary of Product Characteristics (SmPC) in relation to other side effects (www.medicines.org.uk).

Contraindications and Precautions
The use of Fibrovein is not recommended for the treatment of varicose veins when any of the following factors are present: Hypersensitivity to sodium tetradecyl sulfate or to any component of the preparation. Patients unable to walk due to any cause. Patients with a high risk of thrombosis. Recent acute superficial thrombophlebitis or deep vein thrombosis. Varicosities caused by pelvic or abdominal tumours unless the tumour has been removed. Uncontrolled systemic disease such as diabetes mellitus, toxic hyperthyroidism, tuberculosis, asthma, neoplasm, sepsis, blood dyscrasias and acute respiratory or skin diseases. Significant valvular incompetence of the deep veins. Occlusive arterial disease. Huge superficial veins with wide open communications to deeper veins. Phlebitis migrans. Acute cellulitis. Allergic conditions. Acute infections. Bedridden patients. Known symptomatic patent foramen ovale when used as foam.

Special warnings and precautions
Fibrovein should only be administered by a healthcare professional experienced in venous anatomy and the diagnosis and treatment of conditions affecting the venous system and familiar with proper injection technique.

Extreme care in intravenous needle placement and using the minimal effective volume at each injection site are important. Sclerosants must never be injected into an artery as this can cause extended tissue necrosis and may result in loss of the extremity.

Special care should be taken in patients with laboured breathing or a strong predisposition to allergies. Emergency resuscitation equipment should be immediately available. The possibility of an anaphylactic reaction should be kept in mind, and the physician should be prepared to treat it appropriately. Special care is required when injecting the foot and malleolar area where the risk of inadvertent injection into an artery may be increased.

Pigmentation may be more likely to result if blood is extravasated at the injection site (particularly when treating smaller surface veins) and compression is not used.

Patients should have post-treatment follow up of sufficient duration to assess for the development of deep vein thrombosis.

Extreme caution in use is required in patients with underlying arterial disease such as severe peripheral atherosclerosis or thromboangiitis obliterans (Buerger's disease).

When the sclerosant has been converted to foam: Known asymptomatic patent foramen ovale (PFO). Patients with a PFO have been shown to be more likely to suffer from adverse events such as temporary neurological events, visual disturbances and migraine. Previous migraine sufferers should be treated with care. Patients with previous migraine or TIA have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant.

Foam should be administered by a physician appropriately trained in the correct generation and administration of foam. Foam is ideally administered under ultrasound guidance.

Use in pregnancy and lactation
Safety for use in pregnancy has not been established. There are no or limited amount of data from the use in pregnant women. Treatment should be postponed until after childbirth. Fibrovein should be used only when clearly needed for symptomatic relief and when the potential benefits outweigh the potential hazards to the foetus. It is not known whether sodium tetradecyl sulfate is excreted in human milk. Caution should be exercised when used in nursing mothers.

Adverse events should be reported. Information about adverse event reporting in the UK can be found at yellowcard.mhra.gov.uk. Adverse events should also be reported to STD Pharmaceutical Products Ltd.

2 Pharmaceutical Precautions

This medicinal product does not require any special storage conditions. Do not freeze. Keep the ampoule in the outer carton in order to protect from light.

3 Legal Category

Prescription only

POM Packs & Cost
3% 5 x 2 ml £40.38
1% 5 x 2 ml £27.13
0.5% 5 x 2 ml £22.72

4 GB Product Licence Numbers

0398/0212, 0398/0213, 0398/0214.
Fibrovein & STD are registered trademarks.

5 Sold and Supplied by

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