Keywords
Venous adhesive, endovenous treatment, varicose veins, cyanoacrylate adhesive, catheter technique

Summary
Introduction: Treatment of saphenous varicosis with the VenaSeal™ Closure System requires no general or tumescent anaesthesia, nor is there any need for compression stockings to be worn. This paper reports on use, initial experience and 2-year results.

Material and method: From March 2012 to May 2014, 274 saphenous veins in 218 patients were treated with the VenaSeal™ Closure System. Doppler and duplex examinations were performed after 7 days, 6 weeks, 1 year and 2 years. Closure and complication rates, the pain score on a visual analogue scale and the venous clinical severity score (VCSS) were documented.

Results: Follow-up examinations were performed on 227 great saphenous veins (GSVs) and 24 small saphenous veins (SSVs). The closure rate of the GSVs was 99.5 % (n=227) after 7 days, 96.5 % after 6 weeks (n=172), 93.4 % after 1 year (n=61) and 100 % after 2 years (n=20). The closure rate of the SSVs was 100 % after 7 days (n=24), 6 weeks (n=12) and 1 year (n=4). No major complications occurred. Minor complications after treatment of the great saphenous vein were inflammatory reactions in 44 legs and phlebitis in 32 legs. During treatment, the pain score developed from 1.4 to 1.5 (3rd day), 2.1 (5th day), 1.6 (10th day), 0.2 (4 weeks) to 0.1 (6 weeks). Preoperatively, the VCSS was 4.4 and this value fell to 2.9 (7th day), 2.1 (6 weeks) and 1.8 (1 year and 2 years)

Discussion: The VenaSeal™ closure treatment of saphenous varicosis is safe and effective. The results are comparable to those obtained with thermal ablation procedures. In the absence of tumescent anaesthesia, patients have far fewer symptoms compared with thermal ablation procedures, both during treatment and postoperatively.

Schlüsselwörter
Venenkleber, endovenöse Behandlung, Varikose, Cyanoacrylkleber, Kathetertechnik

Zusammenfassung

Material und Methode: In der Zeit von März 2012 bis Mai 2014 wurden 218 Patienten an 274 Stammvenen mit dem VenaSeal™ Closu-re-System therapiert. Doppler und Duplexuntersuchungen erfolgten nach 7 Tagen, 6 Wochen, 1 Jahr und 2 Jahren. Erhoben wurde die Verschluss- und Komplikationsrate, der visuelle analoge Schmerz-Score und der Venous Clinical Severity Score (VCSS).

Ergebnisse: Nachuntersuchten wurden 227 Stammvenen der Vena saphena magna (VSM) und 24 Stammvenen der Vena saphena parva (VSP). Die Verschlussrate der VSM betrug 99,5 % (n=227) nach 7 Tagen, 96,5 % nach 6 Wochen (n=172), 93,4 % nach 1 Jahr (n=61) und 100 % nach 2 Jahren (n=20). Die Verschlussrate der VSP betrug jeweils 100 % nach 7 Tagen (n=24), 6 Wochen (n=12) und nach 1 Jahr (n=4). Majorkomplikationen traten nicht auf. Als Minorkomplikationen traten nach Behandlung der Vena saphena magna inflammatorische Reaktionen bei 44 Beinen und Phlebitiden bei 32 Beinen auf. Der Pain Score entwickelte sich unter der Behandlung von 1,4 auf 1,5 (3. Tag), 2,1 (5. Tag), 1,6 (10. Tag), 0,2 (4 Wochen) auf 0,1 (6 Wochen). Der VCSS betrug präoperativ 4,4 und sank auf 2,9 (7. Tag), 2,1 (6 Wochen) auf 1,8 (1 und 2 Jahr)

Endovenous thermal procedures are increasingly being used in the treatment of saphenous varicosis. They are established procedures and their efficacy has been confirmed in many published studies (1–3). These procedures have to be performed under tumescent or general anaesthesia. The closure rates are comparable to those of vein stripping surgery and the complication rates are low (1–3). With the VenaSeal™ Sapheon Closure System, treatment of saphenous varicosis is now possible without either tumescent or general anaesthesia. No nerve damage or haematoma formation occurs. Compared with thermal procedures, patients’ quality of life is improved, as they can resume their everyday activities, perform sports, drive vehicles and work immediately after treatment. No compression therapy is necessary.

The VenaSeal™ Sapheon tissue adhesive (Vbond™) has had CE approval in Europe since September 2011 for the treatment of saphenous varicosis.

Cyanoacrylate adhesive

Cyanoacrylate adhesive has been used in many areas of medicine in Germany for 50 years (4–6). It is deployed as a haemostatic agent in eye surgery, in dental procedures, for wound adhesion in dermatological procedures and in surgical haemostasis. To date, no carcinogenic or mutagenic effect has been reported for cyanoacrylate (6). The adhesive developed by Sapheon consists of an N-butyl-cyanoacrylate with biocompatible additives. The new composition reduced the polymerisation time, concurrently increased the adhesive’s viscosity, and made the adhesive so flexible and soft as to be no longer perceptible, irrespective of whether the patient is at rest or mobile.

The risk of embolisation has been greatly minimised due to the high viscosity, as the adhesive does not tear. These are all prerequisites to vascular use of the adhesive (7–10). Contact between the tissue adhesive and anionic substances, such as blood cells, the vascular endothelium or blood plasma, leads to polymerisation, which destroys not only the endothelium but also the underlying muscularis (Fig. 1). Histologically, the polymerisation process always leads to an inflammatory reaction in both the vascular wall and the surrounding tissue, with lymphocyte and macrophage influx. During the organisation, intraluminal fibroblast influx occurs, leading to venous restructuring with the formation of connective tissue. Histological sections obtained after 11 months also show a marked macrophage influx into the lumen (Fig. 2).

Studies

Feasibility study

The first feasibility study was performed by Almeida et al. as a prospective, non-randomised, single-centre study in the Dominican Republic in 2011. The primary endpoints were the safety and efficacy of the VenaSeal™ system. Treatment was performed in the refluxive great saphenous vein in 38 patients. 29 patients were female with a mean age of 51 years (range: 26–70) and a mean venous clinical severity score prior to treatment of 6.1 ± 2.7, which fell to 1.5 ± 1.4 after 12 months (p<0.001, t-test).

Prior to treatment, the mean diameter of the great saphenous vein at the saphenofemoral junction was 8.0 ± 2.2 mm (range: 4.1–12.0 mm). Patients were examined in the standing position. The mean length of the treated saphenous vein was 33 cm (range: 15–52 cm). The mean treat-
ment time was 20.3 minutes (range: 11–33 minutes). The mean quantity of adhesive injected into the veins was 1.3 ml (range: 0.63–2.25 ml).

Ultrasound examinations were performed up to 48 hours after the procedure and after 1, 3, 6, 12, 24 and 36 months. Closure rates were 100% up to 48 hours after treatment, 94.5% after 1 year (n=36/38) and 92% after 2 years (n=26/38) and 3 years (n=26/38) (Kaplan-Meier analysis) (11) (▶ Tab. 1).

Postoperative thrombus extensions into the femoral vein were observed in 8 out of a total of 38 (21%) cases. These were no longer visualised in subsequent follow-up examinations. As minor complications, 6 cases of thrombophlebitis occurred, which were successfully treated with non-steroidal anti-inflammatory drugs. Up to 30 days after treatment, 31 out of 37 patients had reported no complications at all. One patient developed hyperpigmentation of the thigh. In this case, the saphenous vein was treated directly under the skin. No severe complications, such as venous thrombosis or pulmonary embolism, were observed.

eSCOPE (European multicentre study)

Seven European venous centres in Germany, Denmark, the Netherlands and England participated in this prospective multicentre study for the treatment of great saphenous vein varicosis with the VenaSeal™ Sapheon Closure System. 70 patients had been enrolled up to September 2012. The primary endpoint of the study was saphenous vein closure. No sedation, tumescent anaesthesia or wearing of compression stockings was necessary. Varicosis of the lateral saphenous branches was not treated during the first 3 months. Ultrasound examinations were performed after 2 days, 1, 3, 6 and 12 months and 1 year. The 24- and 36-month follow-up examinations have not yet been conducted.

Results

For treatment of the great saphenous vein, a mean quantity of 1.3±0.4 ml (range: 0.4–2.2) adhesive was required. Closure rates were 94.3% after 6 months (n=70/70) and 92.9% after 12 months (n=66/70) (Kaplan-Meier analysis) (12) (▶ Tab. 1). No severe complications, such as pulmonary embolism or venous thrombosis, were reported. As minor complications, phlebitis occurred in six patients (8.7%) and five patients (7.2%) were given non-steroidal anti-inflammatory drugs. One patient (0.7%) developed a thrombus extension into the femoral vein, which was no longer visualised at follow-up examination. The venous clinical severity score (VCSS) was 4.4±2.3 prior to treatment and fell to 1.8±1.6 after one month.

VeClose (FDA pre-approval study)

The currently ongoing FDA pre-approval study is a randomised multicentre study comparing the VenaSeal™ Closure System™ with Covidien ClosureFast™ radiofrequency catheter ablation in the treatment of great saphenous vein varicosity. 242 patients had been enrolled up to September 2013. 20 of these patients underwent instruction from Sapheon and were treated with the tissue adhesive and the remaining 222 patients were randomised. 108 patients underwent the VenaSeal™ Closure treatment and 114 were treated with radiofrequency catheter ablation.

The primary endpoint was to obtain results that were at least equally as good as but non-inferior to those achieved with the thermal ablation procedure. During the first 3 months, no further lateral branch treatment was to be performed. The planned study duration is 3 years. Ultrasound examinations are scheduled after 3 days, 1, 3, 6 and 12 months and after 2 and 3 years. The closure rate after 1 month was 100% in the VenaSeal™ group and 86.8% in the Closure Fast™ group. After 3 months, the closure rate was 98.9% in the VenaSeal™ group and 95.4% in the ClosureFast™ group (Kaplan-Meier analysis) (▶ Tab. 1) (13).

Preparation

The VenaSeal™ kit contains a vial with 5 ml adhesive, 2 syringes with two corresponding cannulas, a dilator with an effective length of 86 cm, the adhesive catheter (91.8 cm), an 0.035 guide wire (180 cm long) and a dispenser gun. The adhesive

<table>
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<th>Tab. 1 Study results.</th>
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<tr>
<td>Feasibility Study</td>
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<tr>
<td>▶ 38 Patients, enrollment completed Aug. 2011</td>
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<tr>
<td>▶ Primary endpoints: Safety and efficacy</td>
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<tr>
<td>▶ No adjunctive treatments for 6 months</td>
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<tr>
<td>▶ Closure rates:</td>
</tr>
<tr>
<td>– 1-year, 94.5%, n=36/38</td>
</tr>
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<td>– 2-year, 92%, n=26/38</td>
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<td>– 3-year, 92%, n=29/38</td>
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<td>(Kaplan-Meier analysis)</td>
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<td>eSCOPE (European multicenter study)</td>
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<td>▶ 70 patients, enrollment completed Sept. 2012</td>
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<td>▶ Primary endpoint: closure w/o use of sedation, tumescent anesthesia or compression stockings;</td>
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<tr>
<td>▶ No adjunctive treatments for 3 months</td>
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<tr>
<td>▶ Closure rates:</td>
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<tr>
<td>– 6 Month 94.3% 70/70</td>
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<td>– 12 Month 92.9% 66/70</td>
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<td>(Kaplan-Meier analysis)</td>
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<td>VeClose (U.S. pivotal trial) Randomized Control Trial</td>
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<tr>
<td>▶ 242 Enrolled,</td>
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<td>– 108 VS, 114 RFA = Randomized Cohort</td>
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<tr>
<td>– 20 VS = Roll-in/Training VenaSeal</td>
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<tr>
<td>▶ Primary endpoint: non-inferiority to RFA in GSV closure</td>
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<tr>
<td>▶ No adjunctive therapy before 3 months</td>
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<tr>
<td>– 1 Month VS 100% / RFA 86.8%</td>
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<tr>
<td>– 3 Month VS 98.9% / RFA 95.4%</td>
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<tr>
<td>(Kaplan-Meier analysis)</td>
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The treatment of saphenous varicosity with the VenaSeal™ Closure System can be performed in either a sterile operating theatre or a surgical procedure room. In addition to the VenaSeal™ kit, a small syringe with local anaesthetic, some sterile plates and a needle for venous access are required. Also necessary is an operating table, which can be tilted into both the Trendelenburg and the reverse Trendelenburg position.

The vein to be treated is accessed below the lower point of incompetence by means of ultrasound-guided puncture. The guidewire is pushed forwards over the needle and positioned in the popliteal vein or the common femoral vein if the great saphenous vein is being treated. The puncture site is lightly indicated with the scalpel. The dilator is then inserted over the guidewire and placed in the area of the common femoral vein under ultrasound guidance. The guidewire and the mandrin are then withdrawn and the dilator is then blocked with a syringe with saline solution. Thereafter, under ultrasound guidance, the dilator is withdrawn until it lies 5 cm below the femoral vein and the adhesive catheter is introduced through the dilator.

Care must be taken to avoid kinking in the adhesive catheter with subsequent damage to the inner coating and luminal adhesion. Under ultrasound guidance, the catheter is then placed 5 cm before the femoral vein and the treatment table is set to the five-degree Trendelenburg position. Catheter system placement is performed according to Sapheon's recommendation.

The saphenofemoral junction is then compressed transversely using the ultrasound transducer and 0.10 ml of adhesive are delivered by pressing the trigger of the dispenser gun. It is important to keep the trigger pressed for 2–3 seconds, so that the viscous adhesive is delivered from the catheter. The catheter is then withdrawn 1 cm and another 0.10 ml of adhesive is injected. The catheter is then withdrawn 3 cm.

The proximal great saphenous vein or proximal small saphenous vein is then compressed with the right hand for three minutes. The catheter tip is then located under ultrasound guidance. Due to the air channels in the catheter, the tip can be very easily detected. The vein is then compressed transversely again with the ultrasound transducer, another 0.10 ml of tissue adhesive is injected and manual compression is now maintained for 30 seconds.

This procedure is then repeated as far as the puncture site. When the adhesive catheter becomes visible and protrudes from the tubing for approximately 5 cm, the catheter system is pulled out of the vein with a rapid tug. This is necessary to ensure that the adhesive tears off and is not deposited at the puncture site. The puncture site is briefly compressed and a Steri-Strip™ adhesive plaster is applied.

The length of adhesive supplied with the VenaSeal™ Kit is sufficient to treat a total venous length of approximately one metre.

**Therapeutic indications**

The VenaSeal™ Closure System can be used for the treatment of varicosity of the great and small saphenous veins. It is also appropriate for treating the accessory veins, the femoro-popliteal vein, Giacomini’s vein, perforating veins and in the presence of recurrent varicose veins.

**Author’s own results**

From March 2012 to May 2014, 274 saphenous veins in 218 patients were treated with the VenaSeal™ Closure System. 193 patients underwent adhesive treatment in 245 great saphenous veins and 25 patients in 29 small saphenous veins. Follow-up Doppler and duplex examinations were performed after 7 days, 6 weeks and annually. The closure and complication rates, the visual analogue pain score and the venous clinical severity score (VCSS) were recorded.
The first 41 patients were treated according to the Sapheon recommendations with the catheter tip placed at 5 cm from the deep vein and the adhesive was filled into the catheter up to the marker 3 cm from the tip. Successful treatment was assessed as saphenous vein closure below the entry point of the epigastric vein. Due to the formation of some long stumps (up to 5 cm) during the postoperative period, the protocol was changed. In subsequent patients, the adhesive catheter was filled completely and placed distally to the epigastric vein at a minimum distance of 15 mm. Patients were placed in the supine position for the treatment.

**Treatment of the great saphenous vein**

119 women and 74 men with a mean age of 59 years were treated. The mean body mass index (BMI) was 25.2. 21 extremities were classified as C2, 198 as C3, 25 as C4 and 3 as C5.

The mean venous diameter treated at 1 cm from the femoral vein was 8.2 mm. In 47 cases, the anterior accessory saphenous vein was also treated, and, in 15 cases, the posterior accessory saphenous vein. In 231 patients, the great saphenous vein was accessed below the knee joint, in 14 patients above the knee joint. The mean quantity of adhesive used was 1.36 ml and the mean length of vein treated was 46 cm. The mean duration of treatment was 17 minutes.

Of the 245 treated saphenous veins, colour-coded duplex ultrasound examination was performed on 227 veins after 7 days, on 172 vessels after 6 weeks, on 61 after 1 year and on 20 after 2 years. Postoperatively, eleven patients presented with reflux from the saphenofemoral junction into the saphenous vein. Phlebitis of untreated lateral branches occurred in eight patients, hyperpigmentation in seven patients, inflammation of the saphenous vein in five patients, thrombus extension into the femoral vein in three patients and paraesthesia in two patients. No bruising, ecchymosis or oedema occurred (Tab. 3).

Pain during treatment and the postoperative follow-up period was recorded on the visual analogue scale. The score was 1.4 during treatment, 1.5 after 3 days, 2.1 after 5 days, 1.6 after 10 days, 1.1 after 14 days, 0.2 after 4 weeks and 0.1 after 6 weeks (Tab. 4). The venous clinical severity score was 4.4 preoperatively and fell to 2.9 on the 7th postoperative day, to 2.1 after 6 weeks, to 1.85 after 1 year and was 1.8 after 2 years.

**Treatment of the small saphenous vein**

25 patients were treated with the VenaSeal™ Closure System in 29 small saphenous veins. 19 women and 6 men with a mean age of 58 years were treated. The mean BMI was 23.52. Eight patients were in stage C2 at treatment, 19 in stage C3 and two patients in stage C4. The mean venous diameter of the incompetent saphenous vein was 6.1 mm. In 18 cases, the adhesive catheter was placed in the femoropopliteal vein. The mean quantity of adhesive used was 0.7 ml and the mean length of vein

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>7 days</th>
<th>6 weeks</th>
<th>1 year</th>
<th>2 years</th>
</tr>
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<tbody>
<tr>
<td>Open</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Closure rate</td>
<td>99.5%</td>
<td>96.5%</td>
<td>93.4%</td>
<td>100%</td>
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**Table 2** Closure rate of the great saphenous vein after VenaSeal™ treatment (n=245).

**Table 3** Minor complications after VenaSeal™.

- No complications: 168 (66.3%)
- Pain: 30
- Inflammation: 42
- Thrombus extension: 3
- Oedema: 0

**Fig. 4** Catheter in the transverse ultrasound plane easily detectable due to the air channels.
Discussion

Thermal procedures, such as radiofrequency catheter ablation, and the use of various laser systems are proven procedures that are firmly established in the therapy of varicosis of the great and small saphenous veins. Use of tumescent or general anaesthesia is obligatory. Postoperative compression therapy is essential after stripping operations.

Use of the VenaSeal™ Closure System enables treatment to be performed without either tumescent or general anaesthesia. Moreover, compression therapy is not necessary after the treatment (3). This means that patients can immediately return to work and drive vehicles. They can drive directly to work after the surgical procedure and resume their general daily activities. They can also participate in sport immediately.

The high closure rates after thermal surgical procedures have been confirmed in many studies and are over 91% (1–3, 14) with correspondingly low complication rates. Currently available study data obtained after use of the venous adhesive show equally good results. These vary between 94 and 100% (9). Our own results show an occlusion rate of 94% after six weeks and 100% after one and two years.

We no longer favour treating varicosis of the lateral saphenous branches during the same session. During our involvement as a participating centre in the eSCOPE study, in which it was only permitted to treat the saphenous veins with the venous catheter and not the varicose lateral branches, it was shown that up to 80% of varicose lateral branches resolved without therapy. If necessary, we recommend intermittent treatment of the remaining varicose veins with foam sclerotherapy.

In addition to treating the saphenous veins, we also treat the accessory veins in our department. In the presence of reflux, the entire treatment is performed using the venous catheter. In the absence of reflux, a drop of adhesive is injected by means of direct puncture in the flow to the epigastric vein or great saphenous vein. It is also possible to treat incompetent perforating veins with the tissue adhesive, and this is also performed by means of direct puncture. Currently, 5 ml of tissue adhesive are supplied with the set. This is sufficient for the treatment of two saphenous veins each approximately 50 cm in length.

With regard to intraoperative and postoperative pain sensations, patients treated with the tissue adhesive benefit more in terms of quality of life compared to patients treated with thermal ablation. In their study, Roos et al. (15) cite a mean pain score of 4 on the visual analogue pain scale during treatment with the ClosureFast™ radiofrequency catheter (Covidien). In a clinical study, Pronk (16) compared stripping surgery with endovenous laser ablation under tumescent anaesthesia and determined a mean score of 4.69 on the visual analogue scale.

In our own patient population, this score is only 1.5 during VenaSeal™ therapy. Whereas patients develop minor complications up to the 6th week after thermal surgical procedures, this period falls to 3–14 days in association with VenaSeal™ treatment. 20% of all our patients treated with VenaSeal™ developed no symptoms at all.

Tab. 6  Visual analogue pain scale of the small saphenous vein.

<table>
<thead>
<tr>
<th>Tx</th>
<th>3 days</th>
<th>5 days</th>
<th>10 days</th>
<th>14 days</th>
<th>4 weeks</th>
<th>6 weeks</th>
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<tr>
<td>0.8</td>
<td>0.7</td>
<td>0.6</td>
<td>0.2</td>
<td>0.2</td>
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<td>0</td>
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and reported a score of 0 on the visual analogue pain scale from the time of treatment up to 6 weeks after surgery.

Nerve damage, such as can occur after stripping surgery and thermal ablation procedures (17, 18), does not occur with venous adhesive treatment. Occasionally sensory disturbances occur on the inner thigh due to the inflammatory reaction. Once the inflammatory reaction has subsided, however, these are completely reversible. Moreover, no ecchymoses or haematomas develop after treatment. To date, no allergic reactions to the special constituents of the venous adhesive have been observed.

In my opinion, the large number of inflammatory reactions is due to the fact that saphenous veins also undergo direct subcutaneous treatment with the adhesive. Any form of skin redness was classified as an inflammatory reaction. 24 patients with such skin redness declared that they had experienced subsequent pain, although only 5 required analgesia.

Conflict of interest
The author acts in an advisory capacity for the Sapheon company.

Ethical guidelines
The manuscript was compiled in compliance with national legislation and the current Declaration of Helsinki. The patients’ informed consent was obtained.

References