IMMUCOTHEL®
for recurrence prevention of superficial urinary bladder carcinomas

Patients appreciate the well-tolerated alternative
• less distressing side effects
• effective alternative to BCG
• established treatment in several countries
• easy, no-cost disposal
Pre-sensitization with IMMUCOTHEL® 1 mg

<table>
<thead>
<tr>
<th>TUR</th>
<th>Therapy can be started before or during TUR(^A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apply 1 mg s.c. or i.c. in the forearm (positive skin reaction/DTH desired, but not required)</td>
</tr>
</tbody>
</table>

Instillation therapy with IMMUCOTHEL® 10 mg

<table>
<thead>
<tr>
<th>1(^{st}) – 2(^{nd}) month</th>
<th>Initial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 ml (2 × IMMUCOTHEL® 10 mg) weekly in week 1 – 6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3(^{rd}) – 12(^{th}) month</th>
<th>Maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 ml (2 × IMMUCOTHEL® 10 mg) monthly</td>
</tr>
</tbody>
</table>


Alternative after BCG failure

IMMUCOTHEL® is especially after BCG failure or BCG intolerance advisable. These include severe side effects due to BCG. IMMUCOTHEL® can be an alternative for radical cystectomy in patients, when risks, morbidity, and impaired quality of life outweigh the advantages.\(^1\)

Why pre-sensitization?

Pre-sensitization should be performed at the time of TUR. If no skin reaction occurs, pre-sensitization should be repeated. A recent clinical trial showed that it is advisable to start instillation after four days, even without positive skin reaction.\(^3\) A substantial percentage of patients display no skin reaction. However, the absence of skin reaction does not allow a prognosis regarding treatment response to IMMUCOTHEL®.\(^2\)
Summary of the most important aspects

IMMUCOTHEL® is approved as immunotherapy for the prevention of recurrent superficial bladder carcinoma (Tis, Ta-T1 (G1-G3)) after transurethral resection

- IMMUCOTHEL® is approved for high-risk tumors as second-line treatment or in the event of failure or contraindication of BCG

- Patients appreciate the advantage of comparable effectiveness with significantly fewer side effects compared to BCG therapy

- IMMUCOTHEL® can be combined with one immediate instillation of chemotherapy, mostly Mitomycin C, as recommended in the EAU Guidelines

- Standard therapy with a cytostatic agent or BCG cannot be used in all patients. Side effects, intolerances, or limited availability (BCG) can present limiting factors

- In contrast to cytostatic agents and BCG, IMMUCOTHEL® can be prepared in ready-to-use form without special personal or product protection

- The substance can be disposed of along with normal medical practice waste and does not fall under the cytostatic agent/CMR substance ordinance; this is a logistical advantage in daily medical practice routine

Additional information for KLH/IMMUCOTHEL®:
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Structure of KLH or active component of IMMUCOTHEL®

At a glance

<table>
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<th><strong>KLH</strong> = Keyhole Limpet Hemocyanin</th>
</tr>
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<tr>
<td>Isolated from the hemolymph of the sea snail <em>Megathura crenulata</em></td>
</tr>
<tr>
<td>Cylindrical, copper-bearing blue protein</td>
</tr>
<tr>
<td>One of the largest proteins with 8,000 – 32,000 kDa</td>
</tr>
<tr>
<td>Immunocyanin = active component of IMMUCOTHEL®</td>
</tr>
</tbody>
</table>

An active ingredient from a sea limpet

Immunocyanin is the active ingredient of IMMUCOTHEL®. It is a stable modification of the hemoglobin hemocyanin (Keyhole Limpet Hemocyanin = KLH), which is isolated from the hemolymph of the sea limpet *Megathura crenulata*. The native KLH is a cylindrical, copper-bearing protein. With a molecular weight of 8,000 – 32,000 kDa, KLH is one of the largest existing proteins.

Why is KLH blue?

Two copper atoms in the active center of KLH cause the blue color of the hemolymph. KLH transports oxygen to the tissues comparable to hemoglobin. As hemoglobin carries iron atoms, it is red.
Giant keyhole limpet, a snail from the family of keyhole snails (Megathura crenulata)
The structure of KLH

KLH is big. It is a multidecamer with a molecular weight of 12,000–32,000 kDa. The electronic microscopic image shows that KLH also has a second aggregation type: didecamers with a molecular weight of 8,000 kDa.

Eight functional domains form a KLH subunit (400 kDa), which exists in two different forms: KLH1 and KLH2. These two subunits differ both bio-chemically as well as immunologically. Ten KLH subunits form a decamer (4,000 kDa); the basic unit is the dicamer and the multicamer (Fig. 1). The smallest KLH unit is the functional domain (50 kDa) and it contains the active center.\[^{3,4}\]

KLH is one of the largest known proteins
Structure of KLH

Modified according to:


Fig. 1
What is actually in IMMUCOTHEL®?

As an active ingredient, IMMUCOTHEL® contains immunocyanin, a mixture of the subunits KLH 1 and KLH 2 in a stable modification. Here the native structure of the subunits is completely preserved. Both dicamer and multidecamer KLH forms can be rebuilt again in vitro from IMMUCOTHEL® (Fig. 2).[6]

Composition of IMMUCOTHEL®

Modified according to:

Fig. 2
Preparation of the chromatographic cleaning of keyhole limpet hemocyanin

The blue color comes from copper atoms that bind to the active center of the glycoprotein hemocyanin of the oxygen.
Mechanism of action

At a glance

- IMMUCOTHEL® induces a systemic immune response
- Strong IMMUCOTHEL® immunogenicity is based on the attached oligosaccharides
- Specific antibody reaction against bladder carcinoma cells

IMMUCOTHEL® triggers a strong immune reaction

IMMUCOTHEL® induces a systemic immune response. When the immune system encounters IMMUCOTHEL® for the first time, macrophages are activated. They can immediately act directly against tumor cells. Secondly, macrophages increase the activity of natural killer cells and granulocytes by means of cytokines. Thirdly, macrophages present the antigen with T- and B-lymphocytes for information transfer and at the same time stimulate them by means of cytokines (Fig. 3).
Simplified representation of the immune response using IMMUCOTHEL® therapy

Fig. 3
Why subsequent treatment over a long period?

Using quantitative human anti-KLH ELISA assays, a study in 2012 showed that KLH increased the concentration of several immunoglobulins after an immunization.[6] Older studies demonstrated that the IgM-concentration increased with initial immunization, and then subsequently KLH-specific IgGs increased.

In the treatment-free interval, the IgG titer significantly declined. However, the decrease in IgG- and IgA-concentration reduced after every immunization and resulted in a sustained anti-KLH titer (Fig. 4).[6]

Furthermore, the study was able to show that KLH was not detectable in any of the 35 investigated patients before treatment.[6]

Evolution of anti-KLH antibody concentration after multiple immunization with KLH

Strong immunogenicity due to oligosaccharides

The strong immunogenicity of KLH is probably based on the numerous attached oligosaccharides that account for about 4% of the molecular mass of KLH (Fig. 5). Different mechanisms of action play a role here: on the one hand a non-specific stimulation of the immune system, and on the other hand the stimulation of cytotoxic T-cells. The third mechanism of action is the induction of anti-tumoral antibodies. After an immunization with KLH, mice produced antibodies that bind tumor-associated oligosaccharide antigens. In addition, studies with bladder carcinoma patients showed an increase of anti-KLH antibodies in patients, who responded to KLH treatment.

Strong immunogenicity of KLH due to several oligosaccharides

- Mannose
- Galactose
- N-acetylglucosamine
- N-acetylgalactosamine
- Fucose (only KLH2)

Specific antibody reaction against bladder carcinoma cells

KLH expresses Gal(bbeta 1-3)GalNAc-bearing oligosaccharides.\textsuperscript{[11]} The immunization of rats with KLH induced the production of anti-Gal(bbeta 1-3)GalNAc antibodies. Bladder carcinomas express cross-reactive Gal(bbeta 1-3)GalNAc epitopes (called Thomsen-Friedenreich antigens).\textsuperscript{[12]} Also, Thomsen-Friedenreich antigens are associated with cancer progression and metastasis.\textsuperscript{[13]} Anti-KLH antibodies can bind to the Thomsen-Friedenreich antigens on the bladder carcinoma cell and destroy them (Fig. 6). The effectiveness of immunotherapy with IMMUCOTHEL\textsuperscript{®} for superficial bladder carcinoma is most likely based on this fact.\textsuperscript{[11]}

IMMUCOTHEL\textsuperscript{®} – systemic and specific immune response
KLH antibodies can recognize and destroy bladder carcinoma cells

Modified according to:

Fig. 6
IMMUCOTHEL®
for recurrence prevention

At a glance

Reduced recurrence risk from 70% (TUR) to 30%

Progression risk of only 15%

Tumor downgrading probability 26%

Discovery in the 1970s – KLH reduces recurrence of bladder carcinoma

Already in 1974 Olsson et al. reported that for patients with a recurrent urinary bladder carcinoma, the recurrence frequency after a KLH treatment declined from 70% to 30%.¹⁴ Numerous studies followed, both controlled as well as uncontrolled, which confirmed the recurrence prevention effect of KLH.¹⁵–²⁰

IMMUCOTHEL® – only 30% recurrence rate

In an analysis of six trials (mainly Ta- and T1 bladder carcinomas) with comparable appraisal criteria, the probability of recurrence was 30%.¹⁵–²⁰ Only a small proportion of the recurrences (15%) indicated progression, while downgrading was determined for 26% of the tumors (Fig. 7).¹⁵–²⁰ In many trials, no distinction was made between primary and recurrent tumors for the effectiveness assessment of IMMUCOTHEL®,¹⁵–²⁰ The probability of recurrence of 30% is therefore independent of the risk assessment of the Ta- and T1 bladder carcinomas.
Reduced recurrence risk with IMMUCOTHEL®

<table>
<thead>
<tr>
<th>Percentage [%]</th>
<th>Recurrence-free</th>
<th>Recurrence</th>
<th>Downgrading</th>
<th>Stable</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
</tbody>
</table>

Summary of 6 studies, n = 346

Modified according to:


Fig. 7
IMMUCOTHEL® for recurrence prevention of carcinoma in situ

At a glance

- 49% “long-term disease-free rate” with IMMUCOTHEL®
- Progression risk of only 13%

Carcinoma in situ – a special case

A special case of the superficial bladder carcinoma is the carcinoma in situ (CIS). After a TUR, progression to a muscle-invasive bladder tumor with CIS without further treatment is 54%.

In comparison, only 2% of the patients with a Ta grade one tumor progress to a muscle-invasive bladder carcinoma. Also after treatment with BCG or chemotherapy, the recurrence rate was 34% or 50%, whereby Mitomycin C was more effective in the treatment of CIS than other chemotherapeutics. The “long-term disease-free rate” with a Mitomycin C treatment was 36%, for BCG it is 46%. [21]

An option for carcinoma in situ

IMMUCOTHEL® effectively reduced recurrence of CIS

Several small trials (n=86) have specifically investigated the efficacy of IMMUCOTHEL® for carcinoma in situ (CIS). [22-25] The recurrence rate with an IMMUCOTHEL® treatment was 48%. Progression also declined to 20% (Fig. 8). Especially relevant was the “long-term disease-free rate” of 49%. [22-25]
Comparison of BCG- and Mitomycin C-therapy with IMMUCOTHEL® treatment in CIS

![Bar Chart]

Modified according to:


Fig. 8
IMMUCOTHEL® vs. BCG – immunotherapies in comparison

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</tr>
</thead>
<tbody>
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<td>Frequent side effects result in a discontinuation of therapy with BCG treatment in up to 20% of the patients</td>
</tr>
<tr>
<td>IMMUCOTHEL® recurrence risk is comparable with BCG treatment</td>
</tr>
<tr>
<td>Minor side effect spectrum for IMMUCOTHEL® vs. severe side effects for BCG</td>
</tr>
<tr>
<td>BCG-non-responsive tumors respond well to IMMUCOTHEL®</td>
</tr>
</tbody>
</table>
Severe side effects with BCG treatment

A treatment with BCG is frequently accompanied by severe side effects. The most frequent local side effects are cystitis, disorders in voiding from the urinary bladder and hematuria, which occur in approx. 75% of the patients.

Systemic side effects such as flu-like symptoms, general malaise and fever occur with approx. 40% of the patients. It is recommended to discontinue subsequent instillations in the event of side effects.

Therefore, sometimes only 16% of the patients receive all planned instillations.\(^{[26]}\) Local and systemic side effects result in the discontinuation of the BCG therapy in approx. 20% of the cases.\(^{[27]}\)

To reduce the occurrence of side effects, the following contraindications were compiled for a BCG therapy:\(^{[28]}\)

- TUR within the last 2 weeks;
- traumatic catheter examination;
- macroscopic hematuria;
- urethral stenosis;
- active tuberculosis;
- prior BCG sepsis;
- immunosuppression;
- urinary tract infection.

A BCG treatment is considered to have failed if one or more of the following occurs:\(^{[27]}\)

1) occurrence of a muscle-invasive bladder carcinoma;
2) occurrence of severe papillary tumors and/or CIS after 3 and 6 months;
3) progression during the BCG treatment;
4) BCG-intolerance;
5) severe side effects due to the BCG therapy.
IMMUCOTHEL® vs. BCG – comparable recurrence rate with significantly lower side effects

Only in two studies (n=212) the recurrence rate for IMMUCOTHEL® and BCG was compared directly.\textsuperscript{[17, 20]} These trials showed a slightly increased recurrence rate with an IMMUCOTHEL® treatment, but without statistical significance (44 % vs. 38 %; \textit{p} = 0.4988).\textsuperscript{[17, 20]} A comparison with other studies in which either IMMUCOTHEL® or BCG was investigated also reveals a slightly increased, non-significant probability of recurrence.\textsuperscript{[17, 20]} The greater number of total patients increases the significance of these values, which is also reflected in the lower standard deviation (Fig. 9).

**IMMUCOTHEL® vs. BCG – comparable recurrence risk**

![Graph showing recurrence risk comparison between IMMUCOTHEL® and BCG]

Modified according to:


\textit{Fig. 9}
Minor side effect spectrum for IMMUCOTHEL®

Three trials compared the side effects of IMMUCOTHEL® and BCG for superficial bladder carcinoma. [17,20,29] Side effects associated with an IMMUCOTHEL® treatment were overall significantly less frequent (p < 0.0001) (Fig. 10). In addition, the severity of the side effects induced by a BCG therapy was significantly higher. [17,20,29] Whereas no serious side effects have developed with IMMUCOTHEL® until now, in the case of BCG therapy < 5% of the patients developed serious side effects. [27] Ten patients have since died after an intravesical BCG therapy. [20]

Minor side effect spectrum for IMMUCOTHEL® compared to BCG

<table>
<thead>
<tr>
<th></th>
<th>IMMUCOTHEL®</th>
<th>BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise</td>
<td>7%</td>
<td>33%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>7%</td>
<td>26%</td>
</tr>
<tr>
<td>Increased temp.</td>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>Mild &amp; severe</td>
<td>5%</td>
<td>65%</td>
</tr>
<tr>
<td>Cystitis</td>
<td></td>
<td></td>
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</table>

Modified according to:

Fig. 10
Problem – BCG-non-responsive tumors

If a CIS does not respond to a BCG therapy or if there is progression of other superficial urinary bladder carcinomas, usually a radical cystectomy is recommended, since there is little likelihood that patients will react positively to a further BCG treatment. Furthermore, several studies with conservative therapies such as chemotherapeutics have only delivered disappointing results.

BCG-non-responsive tumors respond well to IMMUCOTHEL®

Two studies have investigated the effect of IMMUCOTHEL® on superficial urinary bladder carcinomas that did not respond to a BCG therapy. 97% of the tumors were carcinoma in situ (CIS). The trials showed that IMMUCOTHEL® was positive for these patients in two respects. Firstly, only 45% of the patients had a recurrence with IMMUCOTHEL®. Secondly, in the case of these recurrences, only 21% of the tumors showed progression.

IMMUCOTHEL® – promising alternative for BCG-non-responsive tumors

Mitrakas et al. investigated the recurrence rate of non-primary bladder carcinomas with a BCG therapy, of which about one third were CIS. The recurrence rate of a further BCG therapy after a failed BCG treatment was 71%. This indicates a significant advantage of IMMUCOTHEL® therapy after a failed BCG therapy compared to a further BCG therapy (45% vs. 71%; p = 0.0074). A comparison of probability of progression for non-primary urinary bladder carcinomas, that were further treated with BCG, to non-primary BCG non-responsive CIS, that were treated with IMMUCOTHEL®, also showed a clear advantage for IMMUCOTHEL® vs. BCG (21% vs. 43%; p = 0.0174) (Fig. 11).
Significant advantage in risk of recurrence or progression with IMMUCOTHEL® in BCG non-responsive non-primary CIS compared to further BCG therapy

Modified according to:

Fig. 11
A look at other application areas

At a glance

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<th>KLH as additive of immunotherapeutic agents in treating cancer</th>
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</thead>
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<tr>
<td>KLH as carrier protein for tumor vaccines</td>
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KLH increases the effect of standard immunotherapeutic treatment of melanomas

McFadden et al. were able to demonstrate in an in vitro study, that KLH had an anti-proliferative effect on melanomas or an additive effect in combination with alpha-interferon and interleukin-2.\[33\] Alpha-interferon and interleukin-2 are both standard immunotherapeutic treatments for melanomas.

Studies conducted on mice have substantiated these results *in vivo*.\[34\] A combination of KLH and interleukin-2 reduced the tumor volume by 30% ($p = 0.014$). With KLH and alpha-interferon, the tumor volume was reduced by 28% ($p = 0.031$).

In contrast, an individual treatment only showed a significant reduction (30%; $p = 0.022$) with interleukin-2, whereas KLH and alpha-interferon reduced the tumor insignificantly by 18% and 16% respectively (*Fig. 12*).\[34\]

Immunostimulating properties of KLH as the basis for tumor vaccines

In the rapidly growing area of tumor vaccines, KLH has special significance. A large number of important tumor associated antigens show poor immunogenicity when injected into humans.
KLH increases the effect of alpha-interferon, a standard immunotherapeutic treatment against melanoma, in vivo

Reduction of the tumor volume [%]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reduction %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-interferon</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>25</td>
<td>0.022</td>
</tr>
<tr>
<td>KLH</td>
<td>20</td>
<td>0.031</td>
</tr>
<tr>
<td>Alpha-interferon + KLH</td>
<td>30</td>
<td>0.014</td>
</tr>
<tr>
<td>Interleukin-2 + KLH</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>


Keyhole limpet hemocyanin: an effective adjunct against melanoma in vivo.

Fig. 12
Increased immunogenicity due to carrier proteins

Immunogenicity of antigens can be increased significantly, when they are conjugated on highly immunogenic protein carriers such as KLH. A large number of cancer antigens have meanwhile been coupled to KLH, creating very promising tumor vaccine candidates, among others against follicular or non-Hodgkin lymphomas, glioblastomas, melanomas, breast and ovarian carcinomas.\[35\]

KLH-coupled tumor vaccines for glioblastoma therapy

Phase I and II studies are meanwhile available for several cancer types.\[36-38\] A phase II study with glioblastoma patients is of particular interest here. Glioblastomas are highly aggressive brain tumors that until now have always ended fatally and non-responsive to available conventional therapies. One of the most frequent genetic changes in glioblastomas is the amplification of the EGFR gene, whereby most changes concern the mutant EGFR gene EGFRvIII. EGFRvIII is expressed in approx. 30% of newly diagnosed glioblastoma patients and is a negative prognostic factor for long-term survival. Eighteen patients were treated with a vaccine against EGFRvIII (PEPvIII-KLH/CDX-110).\[37\] In contrast to the routinely applied chemotherapeutics, the vaccine showed only a minimum toxicity. The duration until progression was significantly prolonged from 6.3 to 14.2 months among the vaccinated patients (p=0.0102).\[37\]

No prolonged survival with KLH-coupled tumor vaccines in phase III trial

The survival time was likewise prolonged from 15 to 26 months (p<0.0001) (Fig. 13).\[37\] In addition, the effect of the vaccination on the standard chemotherapy with temozolomide was investigated. The time period until progression increased from 6.4 to 15.2 months (p=0.0004) or for survival from 15.2 to 23.2 months.\[37\] In the phase III trial EGFRvIII (PEPvIII-KLH/CDX-110) was not associated with a prolonged survival.\[39\] Now therapy combinations are considered to show efficacy of immune therapy in glioblastoma.
No prolonged overall survival with KLH-coupled tumor vaccine in glioblastoma patients in phase III trial

Overall survival median [month]

- Activate (n = 18)
- ACT III (n = 65)
- ACT IV (n = 745)

 EGFRvIII (PEPvIII-KLH/CDX-110)
 Control or placebo group in ACT IV

Modified according to:

Fig. 13
KLH-coupled tumor vaccines for breast cancer therapy

Phase III studies for breast cancer patients with metastases are already available in which the tumor-associated antigen Sialyl-Tn, whose expression is also associated with a poor prognosis among other things for breast cancer, is coupled to KLH.\[^{[40]}\] The study comprised 1,028 women and compared Sialyl-Tn-KLH with KLH alone. Although the Sialyl-Tn-KLH vaccine was well tolerated, there was no significant advantage in the time until progression (3.4 vs. 3.0 months) or survival (23.1 vs. 22.3 months).\[^{[40]}\] However, the authors posed the question whether the clinical advantage had been distorted by using a KLH control group instead of a placebo control group, due to a non-tumor-specific immune response to KLH.\[^{[40]}\] Significantly higher anti-KLH antibody titers in the KLH control group supported this statement.

Prolonged survival in combination with endocrine therapy

A retrospective blinded review of the data from this study also showed that women, who had additionally received a concomitant endocrine therapy, had longer time until progression or survival in the Sialyl-Tn-KLH group (36.5 vs. 30.7 months) (Fig. 14).\[^{[41]}\]
### Prolonged overall survival with KLH-coupled tumor vaccine in metastatic breast cancer patients

<table>
<thead>
<tr>
<th>Overall survival median (month)</th>
<th>p = 0.029</th>
</tr>
</thead>
<tbody>
<tr>
<td>STn-KLH + endocrine therapy</td>
<td>36.5</td>
</tr>
<tr>
<td>unconjugated KLH + endocrine therapy</td>
<td>30.7</td>
</tr>
</tbody>
</table>

Trial (NCT00003638), n = 265


*Fig. 14*
Literature


IMMUCOTHEL® products

IMMUCOTHEL® 1 mg
1 vial with 54.63 mg powder for injections contains 1 mg biotechnically obtained, chromatographically uniform, molecularly standardized immunocyanin.
Each vial is accompanied by 1 ampoule with 1 ml solvent.

IMMUCOTHEL® 10 mg
1 vial with 546.3 mg powder for intravesical instillations contains 10 mg of biotechnically obtained, chromatographically uniform, molecularly standardized immunocyanin.
Each vial is accompanied by 1 ampoule with 10 ml solvent.

Active substance: Immunocyanin

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World market leader for high-dose selenium injections

biosyn Arzneimittel GmbH is a pharmaceutical and biotech company based in Fellbach, Germany. It specializes in trace elements, is a world market leader for high-dose selenium injections, developer and operator of two unique GMP manufacturing operations for producing active ingredients, and in the biotech sector, is actively involved in the production of glycoprotein isolated from the Megathura crenulata, a sea snail found in California. 70 percent of our sales turnover is realized outside of Germany – in 26 countries all around the world.

With products geared to the areas of intensive care, oncology and endocrinology, biosyn is a partner to hospitals and physicians in private practice, as well as to naturopathic physicians and holistic health practitioners. We pursue research and development and evaluate the current medical-scientific literature as well as engage in modern online marketing. Our mid-sized family enterprise places great value on an open, engaged and customer-oriented corporate culture.
IMMUCOTHEL®

for recurrence prevention of superficial urinary bladder carcinomas

biosyn Arzneimittel GmbH
Schorndorfer Straße 32
70734 Fellbach, Germany

www.biosyncorp.com

information@biosyn.de
www.biosynpharma.com
www.biosyn.de

More information about us on our Facebook page and our YouTube channel

Managing Director: Dr. Thomas Stiefel and Ortwin Kottwitz
Commercial Register: County Court Stuttgart HRB 262712
Place of performance: Fellbach, Legal venue Stuttgart