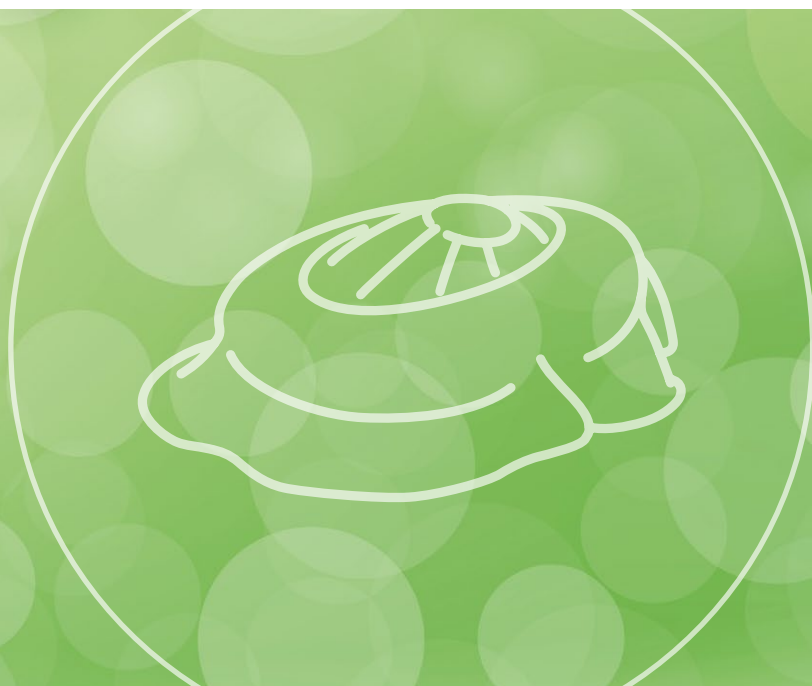


Recurrence-free after IMMUCOTHEL[®] instillation therapy

Case
report



- Initial diagnosis:
urothelial cancer pTa G3 high grade + CIS
- After 5 years:
 - multilocular recurrence pT1G3 high grade
 - TUR plus BCG therapy
 - discontinuation of BCG therapy due to intolerance
- After 11 months of IMMUCOTHEL[®] therapy:
recurrence-free for 3 years with well-preserved
quality of life

The case report was provided by:
Dr. Severin Bauinger, Kepler University Hospital Linz, Austria

we are
research



Case history

A 69-year-old female patient presented at our outpatient clinic in October 2014 with bladder cancer recurrence, cystoscopically confirmed. The patient has been treated in another hospital so far.

Bladder cancer
recurrence

At that time, the patient did not suffer from any concomitant internal diseases and therefore was not taking any long-term medication.

Urological history

- TUR bladder **June 2010** with initial diagnosis of urothelial carcinoma of the urinary bladder pTa G3 high grade + CIS
- BCG instillation therapy for 1 year
- TUR bladder **March 2013** with recurrence of urothelial carcinoma of the urinary bladder pTa G3 high grade



Giant keyhole limpet, a snail from the family of keyhole snails (*Megathura crenulata*)



Course of therapy at our hospital

-
- 2014

 - TUR bladder with photodynamic diagnostics **October 2014** with recurrence of urothelial carcinoma of the urinary bladder pTa G3 high grade.
 - TUR bladder resection **November 2014** without any malignancy detection.
 - The advised re-initiation of an instillation therapy with BCG was rejected by the patient.
 - 2015

 - TUR bladder **May 2015** with multilocular recurrence of urothelial carcinoma pT1 G3 high grade.
 - TUR bladder resection **July 2015** without malignancy detection. Early cystectomy discussed, but now decision to re-initiate BCG instillation therapy. **August 2015** to **September 2015** re-initial cycle of BCG instillation therapy and maintenance therapy of BCG instillation therapy.
 - Termination of BCG maintenance therapy after 3rd month due to side effects: recurrent infections, severe abdominal pain, flank pain.
 - 2016

 - TUR bladder and bladder mapping in cystoscopically suspect findings **February 2016** without malignancy detection, histologically only incipient dysplasia.
 - Rejection of further BCG or chemotherapy (epirubicin / mitomycin) instillation therapy by patient.
 - 2017

 - Start of IMMUCOTHEL® instillation therapy after appropriate presensitization **March 2016** initially for 6 weeks, then monthly until **February 2017**.
 - In the control cystoscopies and bladder flushing cytologies in the period from **March 2016** to **February 2017** no indication of a recurrence of urothelial carcinoma. The patient is discharged from our care, the further tumor follow-up or control cystoscopies are carried out from **March 2017** by the resident specialist for urology.
 - 2018

 - In **December 2018**, a consultation with the patient's attending urologist. **To date**, there has been no recurrence of bladder tumors, the patient is in a very good state of health with inconspicuous micturition conditions after multiple bladder tumor resections and initially BCG and finally 11 months of IMMUCOTHEL® therapy.

Status after IMMUCOTHEL® instillation therapy:

Almost 3 years absence of recurrence with very good quality of life.

List of abbreviations:

- TUR – Transurethral resection
- CIS – Carcinoma in situ
- BCG – Bacillus Calmette-Guérin

IMMUCOTHEL® – an option for non-responsive NMIBC

Two trials investigated the effect of IMMUCOTHEL® treatment on non-muscle invasive bladder cancer (NMIBC) that did not respond to BCG therapy.^[1,2] In these trials, 97 % of the tumors were a carcinoma in situ (CIS). It was demonstrated that IMMUCOTHEL® treatment is positive for these patients in two respects. First, only 45 % of patients undergoing IMMUCOTHEL® treatment had a recurrence.^[1,2] Second, these recurrences only progressed in 21 % of cases.^[1,2]

IMMUCOTHEL® – a promising alternative

Mitrakas et al. investigated the recurrence rate of non-primary bladder carcinomas in BCG therapy, of which about one third were CIS.^[3] The recurrence rate of another BCG therapy after a failed BCG treatment was 77 %. This indicated a significant advantage of IMMUCOTHEL® treatment after failed BCG therapy compared to further BCG therapy (45 % vs. 77 %; $p = 0.0074$).^[1-3]

When comparing the progression probability of non-primary bladder carcinomas further treated with BCG with non-BCG responsive CIS treated with IMMUCOTHEL®, IMMUCOTHEL® therapy showed a clear advantage over BCG treatment (21 % vs. 43 %; $p = 0.0174$) (*Fig. 1*).^[1-3]

IMMUCOTHEL® as second-line therapy – reimbursable in Austria

IMMUCOTHEL® is reimbursable as second-line therapy after standard therapy or for BCG failure or contraindication (yellow box / RE2).

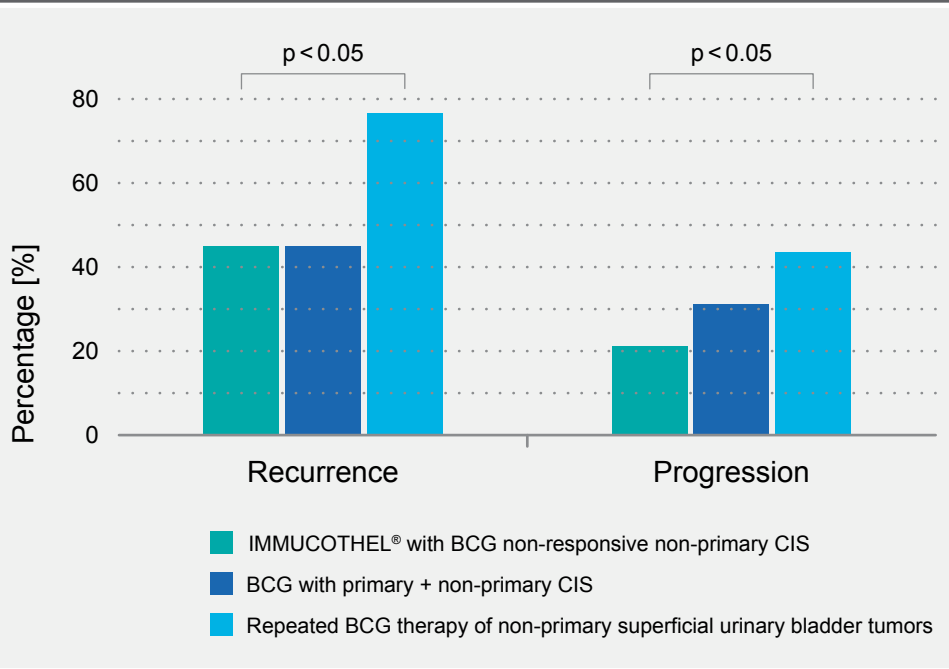
In the refund code:
yellow box / RE2

[1] Bassi P et al. European Urology. 2000; 37 Suppl 2: 113. KLH immunotherapy of BCG resistant carcinoma in situ of the bladder. A phase II trial.

[2] Echarti C, Jurincic-Winkler CD, Klippel KF. Eur Urol. 2000; 37 Suppl 3: 50-3. [Efficacy of prophylactic Immucothel in patients pretreated with conventional drugs to prevent recurrence of superficial bladder carcinoma.](#)

[3] Mitrakas LP et al. Cancer Res Treat. 2015 Jul; 47(3): 495-500. [Previous Bladder Cancer History in Patients with High-Risk, Non-muscle-invasive Bladder Cancer Correlates with Recurrence and Progression: Implications of Natural History.](#)

Significant advantage of IMMUCOTHEL® therapy compared to BCG*



* in BCG non-responsive non-primary CIS compared to further BCG therapy

Modified according to:

Mitrakas LP et al. Cancer Res Treat. 2015 Jul; 47(3): 495-500. [Previous Bladder Cancer History in Patients with High-Risk, Non-muscle-invasive Bladder Cancer Correlates with Recurrence and Progression: Implications of Natural History.](#)

Bassi P et al. European Urology. 2000; 37 Suppl 2: 113. KLH immunotherapy of BCG resistant carcinoma in situ of the bladder. A phase II trial.

Echarti C, Jurincic-Winkler CD, Klippel KF. Eur Urol. 2000; 37 Suppl 3: 50-3. [Efficacy of prophylactic Immucothel in patients pretreated with conventional drugs to prevent recurrence of superficial bladder carcinoma.](#)

Fig. 1

How is the active ingredient of IMMUCOTHEL® obtained?

The active ingredient of IMMUCOTHEL® is immunocyanin, a stable modification of hemocyanin (Keyhole Limpet Hemocyanin = KLH), which is isolated from the hemolymph, the blood of the marine snail *Megathura crenulata*.

The blue color of the hemolymph comes from copper atoms that bind oxygen at the active center of the hemocyanin.

An excursion into modern biotechnology

The hemolymph is extracted at the GMP production facility of the American subsidiary biosyn Corporation in Carlsbad, California, USA. The sea snail *Megathura crenulata* lives exclusively off the Californian coast and is harvested from the cool sea there by special divers.

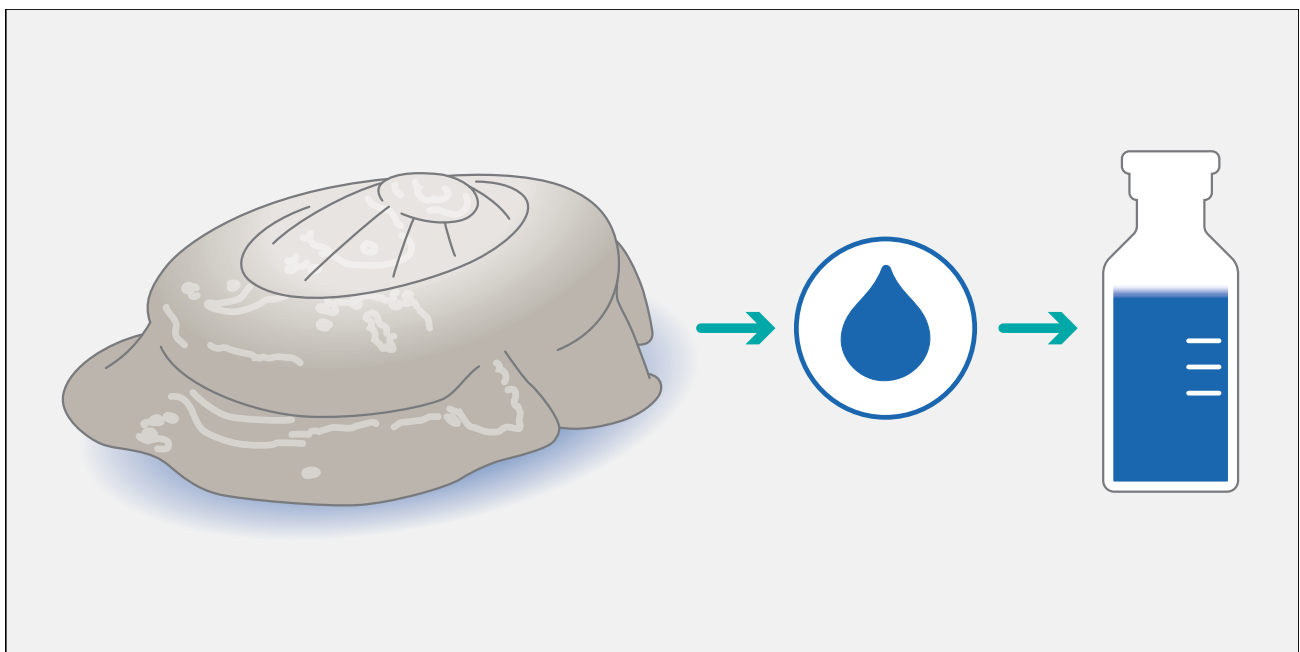
The snail remains a guest of the production plant for two weeks for extraction of the hemolymph. After a quarantine in specially developed aquarium facilities, blood is taken from the snails via the foot after administration of cold anesthesia. The extracted amount of liquid is replenished – how this is done is a company secret. The snails are then returned to the sea undamaged.

The preparation and high purification of the immunocyanin takes place in the production plant of biosyn Arzneimittel GmbH in Fellbach near Stuttgart, Germany, which also complies with the GMP standard.

Over two decades, biosyn has invested millions of euros in research and development of this snail product in the transatlantic project.



[How acts the immunotherapeutic from the sea snail](#) | www.biosyncorp.com



Information on biosyn Arzneimittel GmbH

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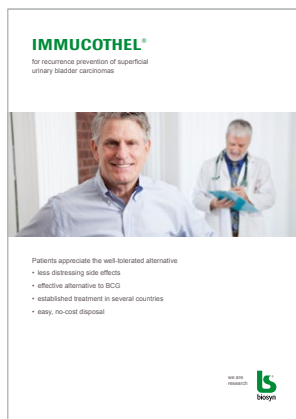
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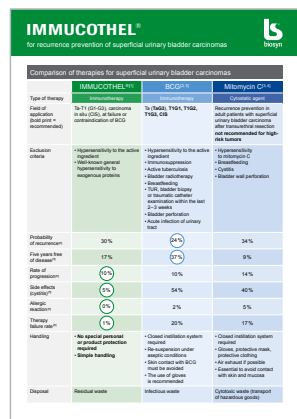
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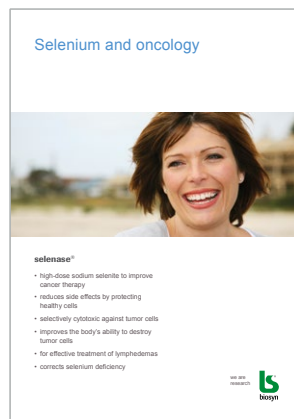
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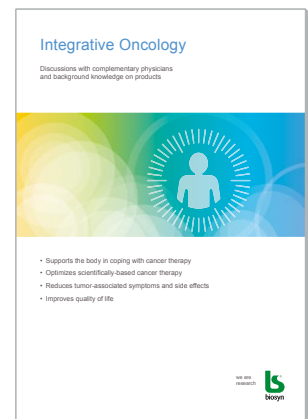
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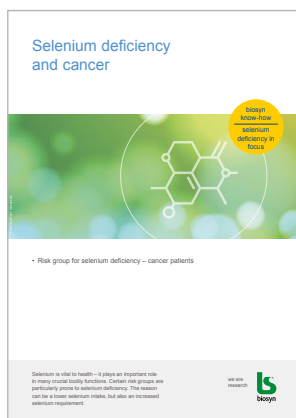
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IMMUCOTHEL® for instillation therapy

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.

Active substance: Immunocyanin



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



IMMUCOTHEL® 1 mg, powder for solution for injection/IMMUCOTHEL® 10 mg, powder for solution for intravesical use

Active ingredient: Immunocyanin. **Indications:** Prevention of bladder carcinoma recurrence after transurethral resection and after failure of established therapies for this indication. **Composition:** 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. **Excipients:** Powder: Glycine, sodium hydroxide, sodium chloride, sucrose. Solvent: Water for injections. **Contra-indications:** Immunosuppression. Known hypersensitivity to proteins foreign to the body. **Undesirable effects:** *Hepatobiliary disorders:* Rare ($\geq 1/10,000$ to $< 1/1,000$): increase of γ -glutamyl transferase and of glutamate pyruvate transaminase. *Renal and urinary disorders:* Rare ($\geq 1/10,000$ to $< 1/1,000$): Urgency, feeling of pressure or pain. Not known (cannot be estimated from the available data): Allergic reactions of the bladder manifesting as sterile leukocyturia. **General disorders and administration site conditions:** Uncommon ($\geq 1/1,000$ to $< 1/100$): Subfebrile temperatures are sometimes reported but are reversible after 3 days. **Interactions:** Specific interactions were not observed. The immunostimulating effect of IMMUCOTHEL® may be impaired by concurrent immunosuppressive radio- or chemotherapy or by simultaneous administration of corticosteroids. **Packages:** IMMUCOTHEL® 1 mg/10 mg: 1 vial of 1 mg/10 mg immunocyanin and 1 ampoule with 1 ml/10 ml solvent. Subject to prescription 03/15 e
Marketing authorization holder: biosyn Arzneimittel GmbH, Schorndorfer Str. 32, 70734 Fellbach, Germany, Tel. +49 711 575 32-00, Fax +49 711 575 32-99, e-mail: info@biosyn.de, www.biosyn.de

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