

Frequently Asked Questions **The Genie Catheter, how does it work:**

Microtubules and paclitaxel:

Microtubules are a component of the cytoskeleton. They are rigid hollow rods approximately 25 nm in diameter. They are dynamic structures that undergo continual assembly and disassembly within the cell. They function both to determine cell shape and in a variety of cell movements, including some forms of cell locomotion, the intracellular transport of organelles, and the separation of chromosomes during mitosis.

Microtubules are composed of a single type of a globular protein, called tubulin. Tubulin is a dimer consisting of two closely related 55-kd polypeptides, alpha and beta tubulin.

Tubulin dimers polymerize to form microtubules, which generally consist of 13 linear protofilaments assembled around a hollow core (= microtubes).

Tubulin dimers can depolymerize as well as polymerize, and microtubules can undergo rapid cycles of assembly and disassembly. Paclitaxel stabilizes microtubules and blocks cells movements and cell division; therefore paclitaxel is used as an anti-cancer drug (Cooper GM, Hausman RE, The Cell, a molecular approach, third edition, 2004, ASM press, p 462-463).

What is paclitaxel's action on a smooth muscle cell ?

It has been determined experimentally that a concentration of 10 micromolar of paclitaxel (roughly 1 mg paclitaxel in 100 ml solution) blocks SMC movements and proliferation but does NOT induce cell death (necrosis), thereby totally avoiding inflammation (Axel in Circulation 1997, Herdeg in JACC 2000, Dommke in Thromb Haemost 2007). In average, when using a 10 micromolar solution of paclitaxel, 2.19 % of the injected amount will remain in the vascular wall (Herdeg in JACC 2000). This means, from Herdeg's ESC 2007 and TCT 2008 presentations (LocalTax and In DES studies respectively), as 13 to 17 ml of a 10 micromolar solution are used for each lesion, 2.19 % of 130 to 170 micrograms of paclitaxel will remain in the vessel wall, which equals to 2.9 to 3.7 micrograms of paclitaxel. As paclitaxel at these concentrations is not cytotoxic, cells remain alive for at least 14 days keeping the paclitaxel incorporated (Herdeg in JACC 2000).

What are the pre-clinical data ?

Animal experiments (pigs) have shown that restenosis is inhibited at a 10 micromolar concentration when applying it to the vessel wall during a short period of time (Herdeg in JACC 2000, Dommke in Thromb Haemost 2007).

Some experiences show that using paclitaxel combined with contrast medium would even work better in preventing cell movements (Scheller in JACC 2003).

Is paclitaxel application safe ?

Animal data show **total endothelialization** at 42 days, without any fibrin deposition or inflammatory response (Dommke in Thromb Haemost 2007) after bare metal stent implantation followed by paclitaxel and Genie catheter treatment. Once total endothelialization has occurred, the risk of thrombosis disappears. This means clopidogrel could be administered for a period of 2 months only after BMS implantation + Genie catheter therapy (instead of 1 y or more for DES).

May paclitaxel be injected directly inside a coronary artery without any damage?

It has been shown in 12 patients that a dose up to 45 mg/m² of paclitaxel (= usually more than 60 mg of total amount of paclitaxel injected inside the coronary artery) may be injected safely into a coronary artery without any damage (Snapist study by Chase and al, Congress of Canadian Cardiology Society 2006). In pr. Herdeg's studies the amounts of paclitaxel injected inside the coronary arteries varied between 130 and 170 micrograms (LocalTax and In DES studies respectively), which is 500 times less than what was established as safe by the Snapist-III study.

Clinical efficacy of paclitaxel applied to a de novo coronary lesion during 2 minutes using the Genie catheter.

Pr. C. Herdeg, from Tuebingen (DE), has recently published in Circulation 2009 the results of a randomized clinical trial performed in Germany showing the efficacy of paclitaxel in 204 patients. It showed equivalent results between patients treated with Taxus stent and BMS combined with Genie therapy (refer to publication: "Catheter-Based Delivery of Fluid Paclitaxel for Prevention of Restenosis in Native Coronary Artery Lesions After Stent Implantation, Circulation 2009").

Clinical efficacy of paclitaxel applied to a in stent (ISR after DES implantation) coronary lesion during 2 minutes using the Genie catheter.

A registry study is currently ongoing in Germany using Genie Catheters and local paclitaxel therapy in restenotic lesions after DES implantation. Forty-nine patients have been implanted so far. Intermediate results are very encouraging showing a 8 % recurrence after this therapy, **without** using a new stent, just by ballooning and treating with the Genie catheter (Herdeg, ESC 2008).

What is the amount of paclitaxel which is injected in the coronary artery during Genie-paclitaxel therapy:

In average, in the Tuebingen *de novo* lesions study, 13 ml of 10 micromolar solution had been used. This means that in average 130 micrograms of paclitaxel have been injected inside the coronary artery during the treatment. This is 500 times (!) less than with 70 mg which are tolerated in the aforementioned study.

Legal Issue about using Paclitaxel?

Any licensed doctor can use Paclitaxel and inject it. Tests have been done on animals, then on human, showing always good results and no harm.

Use of GENIE

Please refer to the Instruction For Use available in the product package. A visual demonstration of the whole procedure is also available on a DVD-format. It is important to recall that Genie **is not a dilatation balloon**. There are **holes** at the surface of the Genie so that the balloon should always **be purged before being used**, by keeping the sleeve in place, and injecting a liquid solution inside until a droplet appears at the catheter tip (very rapidly), then removing the sleeve.

The **indeflator** which is used with the paclitaxel solution **should also be purged** before being used, in order to avoid any air injection during paclitaxel injection.

Preparation of the local paclitaxel solution.

A visual demonstration of the step-by-step preparation of paclitaxel solution is also available on a DVD-format.

All commercially available liquid paclitaxel vials present **the same concentration**, i.e. 6 mg/ml of paclitaxel, independently of the total amount of drug in the vial (30 mg, 50 mg, 100 mg, 300 mg).

Paclitaxel is presented in vials with a 20 mm diameter neck, and a rubber cork on the top. This rubber may be perforated using a needle free vial cap, which allows free sterile picking of the concentrated paclitaxel solution from the commercially available vial.

Commercially available 50 cc saline solution may be used to mix the paclitaxel with it.

After 15 days, one month of use, each commercially available paclitaxel vial has to be sent for microbial monitoring within the hospital institution, and be replaced by a new vial. The safety of multipuncturing the same bottle of paclitaxel during one month was demonstrated by Teva.