# UNOFFICIAL TRANSLATION

## SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

DECAPEPTYL Gyn 3.75 mg
Powder and solvent for suspension for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 4.12 mg triptorelin acetate (1:1), equivalent to 3.75 mg triptorelin, to be suspended in 1 ml solvent enclosed.

For the full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection (sustained release form in pre-filled syringe).

Appearance:
Before reconstitution: white to bright yellow powder and a clear colorless aqueous liquid.
After reconstitution: homogeneous milky-white to bright yellow suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

In assisted reproduction techniques to prevent premature LH surges

Symptomatic uterine myomas when suppression of the ovarian hormonogenesis is indicated as a preoperative measure to reduce the size of individual myomas prior to scheduled myoma nucleation or hysterectomy.

Symptomatic endometriosis confirmed by laparoscopy when suppression of the ovarian hormonogenesis is indicated to the extent that surgical therapy is not primarily indicated.

### 4.2 Posology and method of administration

The medicinal product should only be administered under the supervision of an appropriate specialist having requisite facilities for regular monitoring of response.

The injection of the sustained release form must be performed strictly in accordance with the instructions given in section 6.6.

Following reconstitution, the suspension has to be injected immediately.

**...sology and method of administration**

The dosage of one pre-filled syringe, equivalent to 3.75 mg triptorelin, is injected every 28 days either subcutaneously (e.g. into the skin of the abdomen, the buttock or thigh) or deep intramuscularly. The injection site should be changed each time.

Before start of therapy, preparations containing oestrogen (e.g. oral contraceptives) should be discontinued. In case of uterine myoma and endometriosis, non-hormonal contraceptives should be used during the first treatment month.

*Uterine myoma and endometriosis*
Once every four weeks an injection with one pre-filled syringe, equivalent to 3.75 mg triptorelin. The treatment must be initiated in the first 5 days of the cycle.

*Assisted reproduction techniques*
Single administration on cycle days 2 or 3 (follicular phase) or cycle day 22 (luteal phase).

*Notice for specific patient groups:*
- There is no need to adjust the dose for the elderly.
- According to current data, dose reduction or prolongation of the dosage interval in patients with impaired renal function is not necessary.

**Duration of administration**

*Uterine myoma and endometriosis*
The duration of treatment depends on the initial degree of severity of endometriosis and on the evolution of its clinical manifestations (functional and anatomical) and on the evolution of the volume of the uterine myomas, determined by ultrasonography during treatment. Normally, the maximum attainable result is achieved after 3 to 4 injections.

Due to the possible effect on the bone density, treatment should not exceed a duration of 6 months (see section 4.4).

## 4.3 Contraindications

- Known hypersensitivity against triptorelin, poly(glycolic acid-*co*-lactic acid), dextran or any of the excipients listed in section 6.1.
- Hypersensitivity against gonadotrophin releasing hormones (GnRH) or to another GnRH analogue.
- Pregnancy
- Lactation

## 4.4. Special warnings and precautions for use

Treatment with a GnRH agonist can lead to a decrease of bone mineral density. First data in men suggest that combination therapy of bisphosphonate and a GnRH agonist may reduce the loss of bone mineral density.

Particular caution is advised in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abusers, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticosteroids, family history of osteoporosis, malnutrition).

In rare cases, therapy with GnRH agonists reveals a previously unknown gonadotrophic cell adenoma of the pituitary gland. In these patients, pituitary apoplexy characterised by sudden headache, vomiting, visual disturbances and opthalmoplegia may occur.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as triptorelin. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Mood changes, have been reported. Patients with known depression should be supervised closely.

Allergic and anaphylactic reactions have been observed in adults and children. These include both local reactions at the injection site as well as systemic symptoms. The pathogenesis could not be made clear. The report rate was higher in children.

DECAPEPTYL Gyn should only be prescribed after careful diagnosis (e.g. laparoscopy).

Pregnancy should be excluded prior to initiation of therapy.

Since menstruation is absent during treatment with DECAPEPTYL Gyn, the patient should inform her physician if menstruation continues.

Loss of bone mineral density
The use of GnRH agonists is likely to cause reduction in bone mineral density averaging 1% per month during a six month treatment period. Every 10% reduction in bone mineral density is linked with a two to three times increased fracture risk. In general, the loss of bone mineral density is reversible within 6–9 months after treatment discontinuation.

In the majority of women, currently available data suggest that recovery of bone mineral loss occurs after cessation of therapy.

No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abusers, smokers, long-term treatment with drugs that reduce bone mineral density, e.g. anticonvulsants or corticosteroids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Since reduction in bone mineral density is particularly detrimental in these patients, therapy with triptorelin should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risks following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density.

*Assisted reproduction techniques*
Assisted reproduction techniques are associated with an increased risk of multiple pregnancies, pregnancy loss, ectopic pregnancies and congenital malformations. These risks are also valid with usage of DECAPEPTYL Gyn as adjunct therapy in controlled ovarian hyperstimulation. The use of DECAPEPTYL in controlled ovarian hyperstimulation may increase the risk of ovarian hyperstimulation syndrome (OHSS) and ovarian cysts.

Follicular recruitment, induced by the use of GnRH analogues and gonadotrophins, may be markedly increased in a minority of predisposed patients, particularly in case of Polycystic Ovarian Syndrome.

with other GnRH analogues there have been reports of OHSS associated with the use of triptorelin in combination with gonadotrophins.

Ovarian Hyperstimulation Syndrome (OHSS):
OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.
The following symptoms may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events.
Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore in cases of OHSS it is prudent to withhold hCG and advise the patient to refrain from coitus or to use barrier methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after the hCG administration.

OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum severity at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses.
If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalised and specific therapy for OHSS, e.g. resting, intravenous administration of electrolytes or colloids and heparin, started.

This syndrome occurs with higher incidence in patients with polycystic ovarian disease. The risk of OHSS might be higher with use of GnRH agonists in combination with gonadotrophins than with use of gonadotrophins alone.

Ovarian cysts:
Ovarian cysts may occur during the initial phase of treatment with GnRH agonist. They are usually asymptomatic and non-functional.

*Uterine myoma and endometriosis*
Prolongation of menstrual bleeding during treatment is abnormal (apart from the first month) and should lead to verification of plasma oestrogen level. Should this level be less than 50 pg/ml, possible associated organic lesions should be sought. After withdrawal of treatment, ovarian function resumes, i.e. menstrual bleeding will resume after approximately 7-12 weeks after the final injection.

Non-hormonal contraception should be used during the initial month of treatment as ovulation may be triggered by the initial secretion of gonadotrophins. It should also be used from 4 weeks after the last injection until resumption of menstruation or until another contraceptive method has been established.

During treatment of uterine myoma, uterus and myoma size should be measured regularly by means of, e.g. ultrasonography. Unproportionally rapid reduction of uterine volume in comparison with that of the myoma has, in a few cases, caused bleeding and sepsis.

There have been several reports of bleeding in patients with submucous fibroids after treatment with GnRH analogues. The bleeding usually started 6–10 weeks after initiation of therapy.

DECAPEPTYL Gyn contains sodium, but less than 1 mmol (23 mg/ml) sodium per dose.

## 4.5. Interactions with other medicinal products and other forms of interactions

When triptorelin is co-administered with drugs affecting pituitary gonadotrophin secretion, the patient's hormonal status should be carefully supervised.

No studies on interactions with other medicinal products have been performed. The possibility of interactions with other medicinal products including histamine-releasing substances cannot be excluded.

Interference of calcium antagonists with the mechanism of action underlying GnRH and GnRH analogues is theoretically conceivable. Initial test results on the long-term suppressability of serum testosterone with the depot form of triptorelin during simultaneous therapy with calcium antagonists have, however, provided no evidence of such an interaction.

## 4.6. Fertility, pregnancy and lactation

In women of childbearing potential, pregnancy should be excluded prior to initiation of therapy. Non-hormonal methods of contraception should be employed during therapy until menses resume in women of childbearing potential.

Triptorelin should not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or foetal abnormality. Very limited data on the use of triptorelin during pregnancy do not indicate an increased risk of congenital malformations. However, long-term follow-up studies on development are far too limited. Animal data do not indicate direct or indirect harmful effects with respect to pregnancies or postnatal developments, but there are indications for foetotoxicity and delayed parturition (see section 5.3). Based on the pharmacological effects disadvantageous influence on the pregnancy and the offspring cannot be excluded and DECAPEPTYL Gyn should not be used during pregnancy.

When triptorelin is used for infertility treatment, there is no clinical evidence to suggest a causal connection between triptorelin and any subsequent abnormalities of oocyte development or pregnancy or outcome.

It is not known whether triptorelin is excreted in human milk. Because of the potential for adverse reactions from triptorelin in nursing infants, breastfeeding should be discontinued prior to and throughout administration.

## 4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the ability to drive and use machines may be impaired should the patient experience dizziness, somnolence and visual disturbances being possible undesirable effects of treatment or resulting from the underlying disease.

## 4.8. Undesirable effects

As a consequence of decreased oestrogen levels, the following are the most frequently reported undesirable effects (expected in ≥10% of women): headache, decrease in libido, sleep disturbances, mood changes, dyspareunia, dysmenorrhoea, genital bleeding, ovarian hyperstimulation syndrome, ovarian hypertrophy, pelvic pain, abdominal pain, vulvovaginal dryness, hyperhidrosis, hot flushes and asthenia.

| **MedDRA system organ class** | **Very common (>1/10)** | **Common (≥1/100 and <1/10)** | **Uncommon (≥1/1000 and <1/100)** | **Not known (cannot be estimated from the available data)** |
|---|---|---|---|---|
| Immune system disorders | | Hypersensitivity | Anaphylactic reactions | |
| Psychiatric disorders | Decrease in libido, mood changes, sleep disturbances | Depressive mood, depression | | Confusion, anxiety, |
| Nervous system disorders | Headache | | Paraesthesia | Dizziness |
| Eye disorders | | | Visual disturbances | Blurred vision |
| Ear and labyrinth disorders | | | | Feeling of dizziness |
| Vascular disorders | Hot flushes | | | |
| Respiratory, thoracic and mediastinal disorders | | | | Dyspnoea |
| Gastrointestinal disorders | Abdominal pain | Nausea | | Abdominal discomfort, diarrhoea, vomiting |
| Skin and subcutaneous tissue disorders | Hyperhidrosis | | | Pruritus, rash, angioedema, urticaria |
| Musculoskeletal, connective tissue and bone disorders | Bone pain | Myalgia, arthralgia | Aching of back | Bone diseases(*), muscle cramps, muscular weakness |
| Reproductive system and breast disorders | Vaginal bleeding, vulvovaginal dryness, dyspareunia, dysmenorrhoea, ovarian hyperstimulation syndrome, ovarian hypertrophy, pelvic pain | | | Breast pain, menorrhagia, metrorrhagia, amenorrhoea |
| General disorders and administration site conditions | Asthenia | Tiredness, reactions at the injection site, pain at the injection site, irritation | | Erythema at the injection site, inflammation at the injection site, pyrexia, malaise |

| ystem ss | Very common (>1/10) | Common (≥1/100 and <1/10) | Uncommon (≥1/1000 and <1/100) | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|
| vestigations | | | Blood lactate dehydrogenase increased, gamma glutamyl transferase increased, aspartate aminotransferase increased, alanine aminotransferase increased, cholesterol increased | Blood pressure increased, weight gain, weight loss, |

(*) Slight trabecular bone loss may occur. This is generally reversible within 6-9 months after treatment discontinuation (see section 4.4).

Due to the subsequent administration of gonadotrophins which compensate the adverse events, the symptoms do not last more than a couple of days in assisted reproduction.

Fertility therapy with GnRH analogues may lead to ovarian hyperstimulation. Therefore, follicle growth and luteal phase should be carefully monitored by ultrasonography. Additionally, multiple pregnancies have been reported.

During treatment of uterine myoma, uterus and myoma size should be measured regularly by means of, e.g. ultrasonography.
Unproportionally rapid reduction of uterine volume in comparison with that of the myoma has, in a few cases, caused bleeding and sepsis.

At start of therapy, the symptoms of endometriosis such as pelvic pain, dysmenorrhea may increase during the initial transient rise of plasma oestradiol (very common: ≥10%). These symptoms are transient and usually disappear within one or two weeks after start of therapy.
Genital bleeding including menorrhagia, metrorrhagia may occur within a month after the first injection. Ovarian hypertrophy, pelvic and abdominal pain may occur.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: www.bfarm.de

## 4.9. Overdose

There is insufficient experience of overdosing with triptorelin to draw conclusions on possible adverse effects. Considering the package form and the pharmaceutical form, overdosing is not expected.

In the case of overdosing, treatment should be symptomatical.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Gonadorelin analogues
ATC code: L02AE04

Triptorelin is a synthetic decapeptide analogue of the natural gonadotrophin-releasing hormone (GnRH). GnRH is a decapeptide, which is synthesised in the hypothalamus and regulates the biosynthesis and release of the gonadotrophins LH (luteinising hormone) and FSH (follicle stimulating hormone) by the pituitary. Triptorelin stimulates the pituitary more strongly to secretion of LH and FSH than a comparable dose of gonadorelin, whereas the duration of action is longer. The increase of LH and FSH will initially lead to an increase of serum oestrogen levels. Long-term treatment with a GnRH agonist results in a decrease in FSH and LH secretion by which the oestradiol concentration strongly falls to postmenopausal values, e.g. a hypogonadotrophic hypogonadal state.

Plasma DHEAS (dihydroepiandrostenedion sulphate) levels are not influenced.

The therapy leads to a reduction of oestrogen-dependent uterus myoma and endometriosis foci. Regarding uterine myoma, maximal benefit of treatment is observed in women with anaemia (haemoglobin $\leq$ 8 g/dl).

In assisted reproduction techniques, triptorelin inhibits the preterm LH secretion and following luteinisation of immature follicles.

The suppression profile for the serum estradiol level was the same in women who received the injection in the follicular phase, and in those who received the injection in the luteal phase. The menstruation of the women in the luteal phase started 9 days after single administration and afterwards after abt. 85 days. The menstruation of the women in the follicular phase started 81 days after injection.

### 5.2. Pharmacokinetic properties

After intramuscular injection of DECAPEPTYL Gyn, the plasma concentrations of triptorelin are determined by the (slow) degradation of the poly-(glycolic acid-*co*-lactic acid) polymer. The mechanism inherent to this administration form enables this slow release of triptorelin from the polymer.

After intramuscular or subcutaneous application of a triptorelin depot-formulation (sustained-release microcapsules), a rapid increase in the concentration of triptorelin in plasma is recorded, with a maximum in the first hours. Then the triptorelin concentration declines notably within 24 hours. On day 4 the value reaches a second maximum, falling below the detection limit in a biexponential course after 44 days. After subcutaneous injections the triptorelin increase is more linear and in a somewhat lower concentration than after intramuscular injections. After subcutaneous

ection, the decline in the triptorelin concentration takes longer, with values falling below the detection limit after 65 days.

During treatment over a period of 6 months and an administration every 28 days, there was no evidence of triptorelin accumulation in both modes of administration. Triptorelin values decreased to approx. 100 pg/ml before the next intramuscular or subcutaneous application (median values). It is to be assumed that the non-systemically available proportion of triptorelin is metabolized at the injection site, e.g. by macrophages.

In the pituitary, the systemically available triptorelin is inactivated by N-terminal cleavage via pyroglutamyl-peptidase and a neutral endopeptidase. In the liver and the kidneys, triptorelin is degraded to biologically inactive peptides and amino acids.

40 minutes after the end of an infusion of 100 µg triptorelin (over 1 hour) 3-14% of the administered dose has already been eliminated by the kidney.

For patients with an impaired renal function, adaptation and individualization of therapy with the triptorelin depot-formulation seems to be unnecessary, on account of the subordinate significance of the renal elimination route and the broad therapeutic range of triptorelin.

*Bioavailability:*
After 27 days, 35.7% of the applied dose can be detected on average, with 25.5% being released in the first 13 days and further release being linear at 0.73% of the total dose per day on average.

Calculation of the model-depending kinetic parameters ($t_{1/2}$, $K_{el}$, etc) is inapplicable due to a strongly protracted release of the active component.

## 5.3. Preclinical safety data

In rats treated over a long period of time with triptorelin, an increase in pituitary tumours has been detected. The observation is considered not to be relevant to humans. This is not the case in mice. The influence of triptorelin on pituitary anomalies in humans is unknown. Pituitary tumours in rodents in connection with other LHRH analogues have also been known to occur.

Triptorelin has been shown to be embryo-/foetotoxic and to cause a delay in embryo-/foetal development as well as delay in parturition. Preclinical data reveal no special hazard to humans based on repeat dose toxicity and genotoxicity studies. Single intramuscular or subcutaneous injections of DECAPEPTYL Gyn or its suspension agent produced delayed foreign body reactions at the injection site. Within 8 weeks, these late reactions were nearly reversed after intramuscular injection but only slightly reversed after subcutaneous injection. Local tolerance of DECAPEPTYL Gyn after intravenous injection was limited.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

One pre-filled syringe with powder contains:
poly(glycolic acid-*co*-lactic acid) (1:1), propylene glycol dicaprylocaprate (Ph. Eur.)

*ne* pre-filled syringe with 1 ml solvent for suspension contains:
*D*extran 70, polysorbate 80, sodium chloride, sodium dihydrogen phosphate dihydrate, sodium hydroxide, water for injection.

### *.2.* Incompatibilities

In the absence of compatibility studies this medicinal product should not be mixed with other medicinal products.

### 6.3. Shelf life

3 years

Ready-to-use suspension: 3 minutes.

### 6.4. Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton.

### 6.5. Nature and contents of container

Powder: pre-filled syringe
Suspension agent: pre-filled syringe
Pre-filled syringes (clear borosilicate glass, type I) with a connector (polypropylene), black chlorobutyl rubber stopper (plunger stopper, type I) and injection needle.

Pack sizes:
OP with 1 pre-filled syringe with powder and 1 pre-filled syringe with solvent
OP with 3 pre-filled syringes with powder and 3 prefilled syringes with solvent

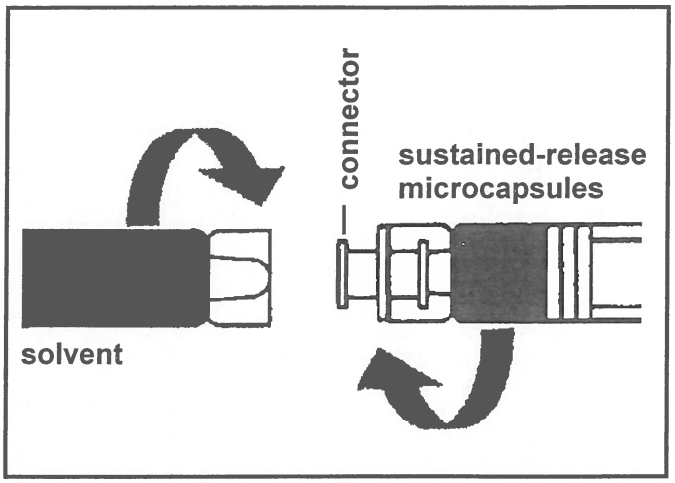
### 6.6. Instructions for use and other handling

DECAPEPTYL Gyn is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**1. Preparation:**
Instructions for the physician how to prepare the suspension:

Since successful treatment depends upon correct preparation of the suspension, the following instructions must be strictly followed.

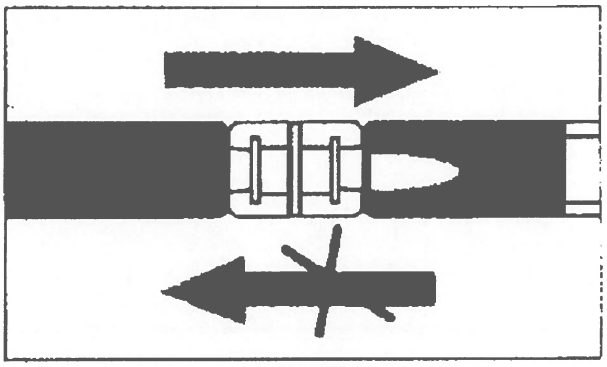
- Take the package of DECAPEPTYL Gyn from the refrigerator.
- Remove the cap from the pre-filled syringe containing the powder. Keep upright to prevent spilling.
- Open the package with the connector **without** removing the connector.
- Screw the pre-filled syringe containing the powder on the connector in the package, then remove it.
- Screw the syringe containing the solvent tightly on the free end of the connector and ensure that it fits tightly.



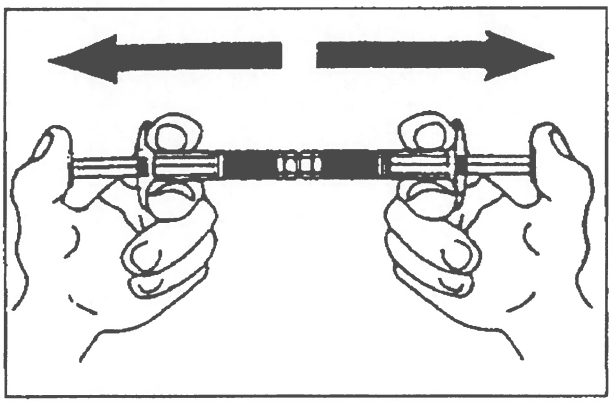

**2. Reconstitution of the ready-to-use suspension:**

- Empty the solvent from the one pre-filled syringe into the pre-filled syringe with the powder, then shoot it back and forth into the first syringe – the first two or three times ***without pushing the injection rod all the way in***.

- Repeat this about 10 times until you have a homogeneous milky-like suspension. While preparing the suspension, you might possibly create some foam. It is important that the foam be dissolved or removed from the pre-filled syringe before giving the injection!



Mixing



mix abt. 10 times

**njection:**

- Remove the connector together with the empty pre-filled syringe.
- Mount the injection needle on the pre-filled syringe with the ready-to-use suspension.
- Inject subcutaneously or deep into the muscle ***immediately***.

## 7. MARKETING AUTHORISATION HOLDER

Ferring GmbH
Wittland 11
D-24109 Kiel

**Codistributor:**
Ferring Arzneimittel GmbH
Fabrikstraße 7
D-24103 Kiel
Tel: 0431-58-52-0
Fax: 0431-5852-74

## 8. MARKETING AUTHORISATION NUMBER

28679.00.00

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

March 10,1995 / June 11, 2002

## 10. DATE OF REVISION OF THE TEXT

March 2015

## 11. PRESCRIPTION/PHARMACY STATUS

Prescription only

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In case of further questions, please contact the following e-mail address: info-service@ferring.de