VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

VI.2.1.1 Prostate cancer

Prostate cancer is the most common cancer in men and the second most deadly cancer in men over

50 years old in the Western world after lung cancer. Every year, thousands of men are affected; about 1 man in 6 will be diagnosed with prostate cancer during his lifetime. This cancer is rare in Asians (but the rate is increasing over the years), common in Europeans, and very frequent in North Americans.

Risk factors most significantly associated with the disease are race (more in black men, than whites or hispanics), age (average age at the time of diagnosis is 70), and family history of prostate cancer. Other risk factors included bladder cancer, vasectomy, and obesity or fat consumption.

In a majority of patients, the cancer of the prostate is using the natural male hormone (testosterone) to develop. The main treatment options are therefore aiming to block the testosterone in order to stop the cancer growth. For patients presenting with aggressive forms of prostate cancer, surgical removal of prostate, radiotherapy, or hormonal therapy (such as triptorelin) are prescribed.

For patients with low-risk forms of prostate cancer, physicians prefer an “active surveillance” strategy: they closely monitor the patients and perform frequent laboratory tests as long as the cancer remains quiet.

VI.2.1.2 Severe sexual deviations

Severe sexual deviations are continual and intense sexual fantasies, urges or behaviours generally involving objects (e.g. fetishism), the suffering or humiliation of oneself or one's partner (e.g. sexual sadism), or children or other non-consenting persons (e.g. paedophilia). The estimation of the number of people affected by a sexual deviation is a challenge. Because of the nature of the disease: shame, religious, moral, legal, and/or familial implications of such deviant sexual behaviour, very few sexually deviant patients voluntarily seek treatment and most of the available data are coming from imprisoned patients or patients admitted in psychiatric hospital based on justice decision.

Generally, paraphilias are far more common in men than in women, and many sexual deviations started during adolescence.

Proper treatment is critical to decrease the number of victims and the risk of recurrence. From a Canadian study on 4,724 rapists and child molesters (no distinction between people with and without diagnosed sexual deviation), it is estimated that 17% of them reoffend after 5 years and 21% after 10 years.

Apart from psychotherapies, the currently available drug treatments for paraphilias included antidepressants for certain types of “mild” paraphilia (e.g. exhibitionism) and paraphilia occurring in adolescent patients, and anti-libidinal hormonal treatments such as steroidal anti-androgens and gonadotropin-releasing hormone (GnRH) analogues (e.g. triptorelin). Historically, surgical castration was used. The combination of psychotherapy and drug therapy is associated with better efficacy compared with either treatment alone.

VI.2.1.3 Endometriosis

Endometriosis is a very common and painful disease where cells from the endometrium, i.e. the uterus, appear outside the uterine cavity. It occurs in 6 to 10% of the women. The causes of endometriosis have not yet been elucidated, but menstruation disorders, immunity disturbances, and genetic factors are suspected. Many women with endometriosis suffer from infertility and need to undergo assisted reproductive therapy to get pregnant.

Risk factors include short menstrual cycle, heavy menstrual volume, young age at time of first periods, high number of pregnancies, cigarette smoking or small body size.

The currently available treatments include pain medications, hormonal treatment, surgery, or a combination of these approaches depending on each woman and on her symptoms, age, fertility, and conception desires.

VI.2.1.4 Central precocious puberty

Precocious puberty is the appearance of secondary sexual characteristics (i.e. breasts or body hair) before age of 8 or occurrence of first periods before age of 9. From about 1 child on 5,000 to 1 child on 10,000 is diagnosed with precocious puberty. Girls are 10 times more frequently affected than boys.

The causes of precocious puberty are most of the time unknown. Brain tumours or lesions, thyroid disorders, or exposure to sex steroids may cause precocious puberty.

In patients with "central" precocious puberty, hypothalamus, a region of the brain, or pituitary, a gland at the base of the brain, is affected. GnRH agonists like triptorelin are the preferred treatment option in this form of the disease and are used to delay puberty until patients attain adolescence.

VI.2.1.5 Early Stage Hormone Responsive Breast Cancer in Premenopausal Women

Breast cancer is the most common cancer worldwide for females. It is also the leading cancer in women in all countries of Europe, with 464,000 cases in 2012. In the EU, about 109 out of every 100,000 people have breast cancer, and there are more cases reported in North and Western Europe than in Eastern Europe. Three quarters of breast cancers respond to hormone treatment and one fifth occur in women who have not yet reached menopause.

VI.2.2 Summary of treatment benefits

VI.2.2.1 Prostate cancer

Triptorelin belongs to a group of medicines called gonadotropin releasing hormone (GnRH) agonists. Triptorelin is similar to the gonadotropin releasing hormone which occurs naturally in the body, but is 100-fold more active than the natural hormone. Among other functions, the gonadotropin releasing hormone can stop the production of testosterone in men.

Hormonal drugs, such as triptorelin, are used in men in the treatment of advanced prostate cancer. By lowering the levels of the male hormone testosterone, triptorelin blocks the cancer development. Triptorelin does not remove the cancer, but stops the tumour growth.

The efficacy of triptorelin is similar to surgical castration. With triptorelin, testosterone is reduced and all functions depending on this hormone are also reduced including the cancer development. The effects of triptorelin are usually reversible after cessation of therapy. Therefore, triptorelin is preferred to surgical castration.

Different formulations of triptorelin are available on the market:

- Triptorelin 3.75 mg, one intramuscular injection administered by a physician or a nurse every month
- Triptorelin 11.25 mg, one intramuscular injection administered by a physician or a nurse every three months
- Triptorelin 22.5 mg, one intramuscular injection administered by a physician or a nurse every six months

The efficacy of the three triptorelin formulations was evaluated in clinical trials involving patients with advanced prostate cancer. The efficacy was defined as the drug's capacity to decrease over several months the body level of the male hormone testosterone under the "castrate" level, meaning a level equivalent or lesser than the level of testosterone in a patient surgically castrated.

The table below summarises the main efficacy results from clinical studies with triptorelin in advanced prostate cancer patients.

Table 73: Main efficacy results from selected clinical trials with triptorelin in advanced prostate cancer patients – Summary for public

Formulation	Triptorelin 3.75 mg	Triptorelin 11.25 mg	Triptorelin 22.5 mg
Treatment schedule	One injection every month	One injection every 3 months	One injection every 24 weeks
Number of prostate cancer patients treated with triptorelin in the selected study*	159 patients	166 patients	120 patients
Study duration	9 months	9 months	48 weeks
Percentage of patients with castrate levels of testosterone 28 days after the first injection	92.5%	97.6%	97.5%
Percentage of patients with maintenance of castrate levels of testosterone	95.3% of patients still castrated after 9 months	94.1% of patients still castrated after 9 months	93% of patients still castrated after 48 weeks

*Results from study DEB-96-TRI-01 (first phase) for the 3.75 mg and 11.25 mg formulations and from study DEB-TRI6M-301 for the 22.5 mg formulatiom

Overall, triptorelin is able to decrease testosterone levels similarly to surgical castration in 92% to 98% of patients (measure 28 days after first injection). Moreover, the effect of triptorelin is maintained:

- over 9 months in 94% and 95% of patients who received one injection every month and every 3 months, respectively, and
- over 48 weeks in 93% of patients who received one injection every 24 weeks.

The clinical trials in prostate cancer patients demonstrated that triptorelin creates a chemical castration over several months, which is as efficient as a surgical castration on the cancer's growth, but without the sequels and traumatism of a surgical intervention.

VI.2.2.2 Severe sexual deviations

By lowering the levels of the male hormone testosterone, triptorelin decreases sexual drive in men. Hormonal drugs, such as triptorelin, are therefore used to decrease sexual drive in adult men with severe sexual deviations. Triptorelin does not substitute to psychotherapy and does not treat the psychiatric condition in itself, but the treatment stops deviant sexual urges helping the patient not to reoffend and to be more receptive to psychotherapy.

Thirty-six (36) men with severe sexual deviations (e.g. paedophilia) were treated with triptorelin acetate at a dose of 3.75 mg in the frame of two clinical trials. Triptorelin administration reduced testosterone to levels similar to surgical castration in all patients. A concomitant decrease in deviant sexual behaviour and fantasies was reported. Abrupt withdrawal of triptorelin treatment led to proven recidivism in a total of 3 patients.

A formulation of triptorelin different from the one used in the studies was registered and is currently available on the market: triptorelin embonate at a dose of 11.25 mg. This formulation is as efficient as triptorelin 3.75 mg formulation in achieving and maintaining castration in men, but is acting over 3 months instead of 1 month. The patient with sexual deviation receives one intramuscular injection of triptorelin embonate 11.25 mg every 3 months by a physician or a nurse and his testosterone remains at a castrate level over the 3 months, meaning his sexual drive is lowered over the 3 months. This is expected to help the patient to better accept a continuous treatment with triptorelin since it is less burden for him to inject only 3-monthly, and therefore by extent to avoid treatment withdrawal and potential recidivism.

VI.2.2.3 Endometriosis

Similarly to its action in men (i.e. reduction of testosterone), triptorelin is able to decrease the female hormones, oestrogens, in women. The cells causing endometriosis depend on oestrogens to grow. By decreasing oestrogens, triptorelin weaken the cells involved in endometriosis and the endometrial lesion and the pain caused by those lesions consequently diminishes.

In the study by Choktanasiri et al. (1996) [43], 45 women with endometriosis were treated with triptorelin 3.75 mg every 4 weeks. The efficacy results of this study are summarised in the table below.

Table 74: Efficacy results of the study by Choktanasiri et al (1996) in women with endometriosis treated with triptorelin

Treatment	**Treatment schedule**	Triptorelin 3.75 mg every month for a total of 6 doses
	Number of endometriosis patients treated with triptorelin	45 patients
	Study duration	24 weeks
Study results	**Percentage of patients with postmenopausal oestradiol level** [40 patients]	100% (after 2 months of treatment)
	Percentage of patients free of severe and moderate pain [43 patients]	85% (after 6 months of treatment) 15% of patients still experienced mild pain
	Percentage of patients with reduced endometriosis severity as per laparoscopic assessment [25 patients]	84%
	Percentage of patients with decreased size of ovarian endometria [9 patients]	89%

In all tested patients, the female sex hormone, oestradiol, decreased after 2 months of triptorelin treatment to a level similar to that of women with menopause. In parallel, pain, endometriosis severity and size of the endometrial lesion decreased. Triptorelin is efficacious in the treatment of endometriosis and relieves the disabling symptoms of the disease.

VI.2.2.4 Central precocious puberty

Children with CPP are producing sexual hormones before the normal age for sexual maturation and consequently they develop breasts, body hairs or periods. Through the same mechanism as in adults, triptorelin decreases sexual hormones in the treated children until they reach a normal age for puberty. A consequent regression of secondary sexual characteristics occurs. Efficacy data from three studies in children with precocious puberty are summarised in the table below.

Table 75: Efficacy results from three studies in children with CPP treated with triptorelin

Formulation	Triptorelin 3.75 mg	Triptorelin 11.25 mg	Triptorelin 22.5 mg
Treatment schedule	One subcutaneous injection every 6 weeks or one intramuscular injection every 4 weeks	One injection every 90 days	One intramuscular injection every 24 weeks
Number of patients treated with triptorelin in the selected studies*	46 girls (26 girls treated every 6 weeks and 20 treated every 4 weeks)	19 girls and 1 boy	39 girls and 5 boys
Study duration	1 year	2 years	48 weeks
Percentage of patients with low luteinizing hormone (LH) levels while on triptorelin (i.e. normal levels for a child)	100% (at 2 months)	100% (at 6 months)	93% (at 6 months)

* (Liang et al, 2006 [151]; Martinez-Agayo et al, 1994 [162]; Debio 8206-CPP-301 clinical study report, 2015)

Triptorelin at 3.75, 11.25 and 22.5 mg induced pituitary suppression with consequent decrease of LH to prepubertal levels for a child in 93-100% studied patients with precocious puberty.

Consequently, improved growth and decreased sexual secondary characteristics (e.g. breast or testicular volume reduction) were observed. In the Martinez-Aguayo study [162] six months after discontinuation of GnRH therapy, 15 out of 16 carefully followed patients had peak LH responses in the pubertal range. Oestradiol and uterine length had risen from 5.8 ± 0.4 pg/ml to 15.4 ± 2.2 pg/ml (p'= 0.004), and 3.8 ± 0.2 cm to 5.1 ± 0.3 cm (p = 0.008) respectively, and breast development had progressed in 4/15 girls, showing the recovery of the HPG-axis. After completion of the Debio 8206-CPP-301 study the patients continued in general to be treated with another GnRH triptorelin or another GnRH agonist locally approved in CPP.

VI.2.2.5 Early Stage Hormone Responsive Breast Cancer in Premenopausal Women

Triptorelin suppresses ovaries from producing oestrogen, a hormone that these types of breast cancers use to grow. The efficacy and safety of triptorelin, with either exemestane or tamoxifen, in the treatment of early stage hormone responsive breast cancer was investigated in two trials (SOFT and TEXT). A total of 4690 premenopausal women were treated with ovarian suppression plus either exemestane or tamoxifen for 5 years. Oestrogen production was suppressed with triptorelin, surgical removal of the ovaries (oophorectomy) or ovarian irradiation.

The main efficacy measure (primary end point) was the number of patients who achieved disease free survival 5 years after entering the study.

On average, patients were followed up for 68 months. After 5 years, over 87% of patients in both treatment groups achieved disease free survival (i.e. the breast cancer had not recurred and a second cancer had not developed).

These studies showed that the treatments reduced the risk of the breast cancer recurring.

Around a tenth of the patients treated by ovarian suppression in SOFT did not receive triptorelin, and fewer than expected patients died or had disease recurrence. Further analysis of these studies will be conducted when the data are more mature.

VI.2.3 Unknowns relating to treatment benefits

Based on a post-marketing experience of over 30 years, mostly in the indication of prostate cancer, the efficacy of the different formulations of triptorelin in inducing reversible reduction of sex

hormones is widely recognised.

The potential effects of triptorelin in pregnant/breastfeeding patients have not been tested. Since animal studies have demonstrated effects on reproductive parameters, pregnant/lactating women must not be exposed.

Patients with hepatic (liver) or renal (kidney) impairment were excluded from both breast cancer studies (SOFT and TEXT); therefore experience in these populations is limited.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Bone loss leading to an increased risk of fracture (Bone loss, osteoporosis and fractures)	Triptorelin blocks some hormones as part of its mechanism of action (e.g. to stop the cancer growth), but these hormones are also involved in the maintenance of bone health. Loss of bone minerals is therefore a common consequence of triptorelin treatment. In most cases, the patients do not present any symptoms, but they have an increased risk of fractures. Risk of hip fracture, for example, is twice higher in a prostate cancer patient under hormonal treatment as compared to an untreated person of the same age and gender. Women are particularly at risk for bone loss since they are already 4 times more prone to osteoporosis than men. Bone loss following GnRH agonist treatment was also observed in children with precocious puberty, but this effect was fully reversible and preventable.	In all patients, the use of preventive concomitant treatment helps in limiting bone demineralisation and therefore lowers the risk of fractures. Additionally, lifestyle modification including smoking cessation, moderation of alcohol use, regular exercise, adequate diet (calcium, vitamin D) are recommended. Patients with endometriosis who already suffer from osteoporosis must avoid taking triptorelin. Patients with paraphilia and already suffering from serious osteoporosis must avoid taking triptorelin.
High blood sugar and high blood lipids which may lead to an increased risk of diabetes (Metabolic changes such as increased fat mass and insulin resistance leading to increased risk of diabetes)	The hormones blocked by triptorelin as part of its mechanism of action, regulate some metabolic processes. Administration of triptorelin results in increase of the blood glucose levels and blood lipid levels. Increases in blood glucose and changes in fat mass can lead to diabetes in predisposed patients (e.g. patients with family history of diabetes or with overweight). Diabetes has however been rarely observed in less than 0.1% of patients enrolled in studies with triptorelin. Since it is a serious condition, a close monitoring with regular blood test is recommended to detect and treat early if a potential sign of diabetes is observed.	Monitoring for early symptoms with regular blood test and early intervention can help preventing the occurrence of diabetes. In addition, lifestyle and/or dietary modifications can be considered.

Risk	What is known	Preventability
Heart and blood vessels diseases (Cardiovascular diseases)	Triptorelin is associated with metabolic changes such as high blood sugar and high blood lipids. An increase in blood lipids may lead to an increased risk of cardiovascular problems in predisposed patients. The exact mechanism has still not been elucidated and all studies were in prostate cancer patients. The association of triptorelin with cardiovascular disorders is controversial, because most men with prostate cancer are old, with either known cardiovascular disease or risk factors for their development. Hypertension has been observed in less than 1% of patients enrolled in studies with triptorelin. However, no increased risk of dying from a cardiovascular disease has been observed in the treated patients. There is no evidence that a similar risk exists in women treated for endometriosis and children treated for CPP. Moreover, those patients are younger than prostate cancer patients and exposed to low doses of triptorelin. As for the risk of diabetes, a close monitoring with regular blood test is recommended to detect and treat early if a potential sign of cardiovascular disorder is observed.	Monitoring for early symptoms can help preventing the occurrence of cardiovascular diseases. In addition, smoking cessation, lifestyle and/or dietary modifications are recommended. Aggressive treatment for high blood lipids is currently not recommended because the relationship between adverse cardiovascular events and the hormonal treatment is not sufficiently understood. For patients with previous cardiovascular disease, a strict compliance to their treatment for cardiovascular disease is recommended and, if any symptoms develop, addition of other drugs should be considered.
Increase of signs and symptoms of the prostate cancer such as pain, possible compression in the spine, or obstruction of the urinary tract (Tumour flare (including metastatic pain, spinal cord compression and urethral obstruction))	In prostate cancer patients, triptorelin, like other GnRH agonist drugs, takes some time to install castration and therefore stop cancer progression. During this time of adaptation of the cells (~1 week), the level of testosterone increases before going down. As a consequence of this temporary testosterone elevation, some patients (≤5%) experience a worsening of signs and symptoms of their cancer and a momentary increase of cancer- related pain. This usually resolves after 1 or 2 weeks. Patients suffering from vertebral metastases and patients with urinary tract obstruction should be carefully monitored at the beginning of treatment, because potential compression of the spine or renal disorder may occur as a consequence of testosterone rise.	This disease is preventable by the administration during the first phase of treatment of an anti- androgen drug that neutralises the increase in testosterone and therefore the potential worsening of cancer symptoms. Administration of pain medications for cancer-related pain, if needed, is also recommended. Additionally, a close monitoring of patients with additional risks (patients with vertebral metastases or urinary tract obstruction) must be performed to detect early and immediately treat if any complication occurs.
Allergic reaction (Hypersensitivity)	Triptorelin, like most of the drugs, can cause allergic reactions in some cases. Few very severe cases (anaphylactic reactions) were reported. Allergic reactions are rare and occurred in less than 0.1% of patients enrolled in studies with triptorelin.	Patients who are allergic to GnRH, GnRH agonists (such as triptorelin) or any compound included in the drug product must not be treated with triptorelin.

Risk	What is known	Preventability
Difficulties with erection and loss of sexual desire (Erectile dysfunction, impotence, decreased libido)	Triptorelin blocks some hormones as part of its mechanism of action (e.g. to stop the cancer growth), but these hormones are also involved in erection and sexual desire in men. Erection difficulties and loss of sexual desire are therefore common consequences of prostate cancer treatment, in about 3-4% of patients treated in studies with triptorelin. Upon withdrawal of treatment, a normal sexuality returns with the male hormone increasing to normal levels. This effect explains triptorelin efficacy in paraphilic patients (e.g. paedophiles), where it is the intended use, i.e. loss of deviant sexual desire.	A concomitant psychological therapy or couple support may be useful to limit the potential consequences of these changes in sexual life.
Mood changes/ depression (Mood changes/ depression, including severe depression)	The patients treated with drugs blocking sex hormones tend to develop depression. Depression was reported in less than 1% of patients treated with triptorelin in the clinical studies. The male diseases treated with triptorelin (prostate cancer and paraphilia) are related with an already increased risk of depression. This background risk is less clear in endometriosis patients or children with precocious puberty.	A close monitoring of patients with pre-existing depression is recommended in order to adapt antidepressant therapy if needed.
Slipping of bones at the hip level in children/adolescents occurring after treatment stop (Slipped capital femoral epiphysis following withdrawal of treatment)	In some adolescents or children treated with GnRH agonists for CPP, cases of bone slipping occurring at the hip level were reported. This is the most frequent hip disorder in children/adolescent. It normally occurs more in boys and obesity or growth disorders are known to be associated with this bone slipping. The cases reported with GnRH agonists were mainly occurring in girls with normal weight and height. The suggested mechanism is that treatment with GnRH agonist, by maintaining low oestrogen levels to stop puberty in children, is weakening the bones at the hip level. When the children reach a normal age for puberty, the GnRH agonist treatment is not necessary anymore and is stopped. The patients then start growing rapidly and this could cause the bones at the hip level to slip. A surgery is necessary to fix the bone back at the right place.	The growth of patients with precocious puberty should be closely monitored to early detect symptoms of bone slipping and therefore prevent such event to occur.
High blood pressure (Hypertension)	Cases of high blood pressure have been reported in breast cancer patients treated with triptorelin in combination with either tamoxifen or an aromatase inhibitor.	Premenopausal women with breast cancer receiving triptorelin in combination with either exemestane or tamoxifen should have regular monitoring of their cardiovascular risk factors and blood pressure.
Blood clots (Thromboembolic events)	A clot in a blood vessel is a common adverse reaction reported with triptorelin in combination with tamoxifen or exemestane.	Warnings are provided in the SmPC and package leaflet to educate patients of this possible side effect.

Risk	What is known	Preventability
Bleed in the brain or lack of blood supply to the brain (Cerebral ischaemia and CNS haemorrhage)	Bleeding in the brain and lack of blood supply to the brain are uncommon adverse reactions in patients with breast cancer receiving triptorelin in combination with tamoxifen or exemestane.	Premenopausal women with breast cancer receiving triptorelin in combination with either exemestane or tamoxifen should have regular monitoring of their cardiovascular risk factors and blood pressure.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Suicide attempt	The patients treated with drugs blocking sex hormones tend to develop depression. Depression was reported in less than 1% of patients treated with triptorelin in the clinical studies. In theory, a patient with known depression can experience a worsening of his/her state leading to suicidal ideation and/or suicide attempt in worst cases. This risk is however potential, since data from surveillance of patients treated with triptorelin revealed only 6 suicide attempts and 3 completed suicides over 30 years of surveillance. Moreover, the treated diseases are already risk factors for suicide. Diagnosis of cancer for example is a strong risk factor for suicide; studies revealed that the risk of suicide is 4 times higher in a patient diagnosed with prostate cancer (treated with any drug or untreated) as compared to someone of the same age and gender. A close monitoring to better define this potential risk is however in place and caution is required when administering triptorelin to patients with a medical history of depression.
Cardiac rhythm changes with therapy decreasing testosterone(QT interval prolongation with the use of androgen deprivation therapy)	Besides the known increased risk of cardiovascular disorders described above, a specific type of cardiac rhythm change, known as 'QT interval prolongation', has been described in 2 clinical studies in patients with prostate cancer. In these studies, the heart rhythm of prostate cancer patients, treated with drugs aiming to decrease their testosterone or who were surgically castrated, was measured. In both studies, cardiac rhythm changes were recorded. In particular, the 'QT interval' of the heart was found to be prolonged. No patients enrolled in those 2 studies presented with medical consequences of this hearth rhythm change, but this condition could be very serious. Indeed, a change in cardiac rhythm is potentially fatal. The cardiac rhythm was observed to be similarly affected by all prostate cancer treatments (e.g. GnRH agonist, GnRH antagonist, or surgical castration) and the physicians think that these changes could be directly related to the reduction in testosterone; meaning directly related to the mechanism of action of the prostate cancer therapies. Triptorelin was not used in those studies and the review of triptorelin cases was not conclusive. However, as a precaution and since this cardiac rhythm change was thought to be related to the reduction in testosterone, the potential risk 'cardiac rhythm changes with therapy decreasing testosterone' is followed and described in the Patient Information Leaflet. A close monitoring of this event is in place and further data need to be gathered to better define this potential risk. Based on what we currently know, caution is required in patients with heart rhythm problems (irregular heartbeat) or treated with other medications known to influence the heart rhythm (e.g. quinidine, procainamide, amiodarone, sotalol). This information is included in the Patient Information Leaflet and in the prescribing information for the doctors.

Risk	What is known (Including reason why it is considered a potential risk)
Controllability of return of normal puberty (Earlier or later than expected puberty/menarche after treatment cessation in precocious puberty with triptorelin 22.5 mg 6-month formulation)	A resumption of normal puberty is expected after treatment cessation with the triptorelin 22.5 mg 6-month formulation similarly to the approved triptorelin 1- and 3-month formulations, with a return of normal puberty with menarche in girls in average around one year after treatment discontinuation. However, no follow-up data from pivotal Study Debio 8206-CPP-301 with triptorelin 22.5 mg are available. At the end of the 48-week study the children were switched on a GnRH agonist locally approved in CPP. Triptorelin 6-month formulation provides similar residual triptorelin levels than those published from two studies with triptorelin 3-month formulations in treatment of CPP, and somewhat higher residual levels were reported from one study with a triptorelin acetate 1-month formulation. There was no accumulation in triptorelin serum levels after the second injection of triptorelin 6-month formulation showing that there was no relevant triptorelin release after 6 months that could potentially prolong the efficacy.
Over active ovaries (Ovarian hyperstimulation syndrome)	Cases of ovarian hyperstimulation syndrome have been reported with use of triptorelin in the treatment of female infertility. Based on what is known about how triptorelin works, it could be a risk in premenopausal women with breast cancer receiving triptorelin in combination with aromatase inhibitors or tamoxifen. Ovarian hyperstimulation resolves spontaneously after 2 to 3 weeks of treatment.
Harm to an unborn baby (Teratogenic effects)	Patients who are pregnant or breast-feeding are not allowed to use triptorelin (i.e. they are contraindications of triptorelin treatment). Triptorelin should not be used during pregnancy because there is a risk of harm to the unborn baby.
Using the product incorrectly (Medication error)	Patients should receive triptorelin injections from a healthcare professional. Since doctors oversee the prescription and administration of triptorelin, the potential risk of medication errors is minimised. The package leaflet contains clear instructions for healthcare professionals on how to prepare and administer the treatment.

Missing information

Risk	What is known
There is very limited information on triptorelin use in pregnant or breastfeeding patients.	Studies in animals with high doses of triptorelin have shown effects on pregnancy in rats. It is unknown whether the currently available low doses of triptorelin may have an effect on pregnancy in humans or pass into breast milk. Since there is no data on this topic, pregnant or breastfeeding women must not receive triptorelin. A pregnancy test must be performed before starting triptorelin and contraception (non-hormonal) must be undertaken during triptorelin treatment. Breastfeeding must be stopped before starting triptorelin and during treatment.
Use in patients with hepatic impairment (liver disease)	The experience with triptorelin in patients with liver disease is limited.
Use in patients with renal impairment (kidney disease)	The experience with triptorelin in patients with kidney disease is limited.

VI.2.5 Summary of risk minimisation activities by safety concern

No additional risk minimisation measures are in place for the important identified risks apart from the routine ones (e.g. patient information leaflet).

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 76: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
7.0	19-Apr-2017	Important identified risks added: • Hypertension • Thromboembolic events • Cerebral ischaemia, central nervous system haemorrhage Important potential risks added: • Controllability of return of normal puberty • Ovarian hyperstimulation syndrome • Teratogenic effects • Medication error (incorrect route of administration) Important missing information added: • Use in patients with hepatic impairment • Use in patients with renal impairment	Newly identified risks, potential risks and missing information added following inclusion of the new Breast Cancer indication, and harmonisation with the IPSEN RMP update. The important potential risk of controllability of return of normal puberty for the 6-month formulation in the paediatric CPP indication was added following a request from BfArM in the Final Variation Assessment Report of the CPP variation. Updated information in previously existing indications (i.e., additional co-morbidities, data on mortality/morbidity) has also been added for completeness and to comply with the RMP template. This newly added information does not result in additional safety concerns.
6.0	10-Jun-2015	Modifications of the risk minimisation measures on the potential risk 'QT interval prolongation with the use of ADT' following PRAC recommendations on this class- effect (EU SmPC sections 4.4, 4.5. and 4.8).	-
		-	Inclusion of the results from 2 completed clinical trials (Debio 8206-SC-301 & Debio 8206-CPP-301).
5.0	04-Jul-2014	Corrective version to perform the following changes: Table in section III.1 'Safety concerns and overview of planned pharmacovigilance actions' was revised to remove the references to the SmPC. In section VI.2.1 'Overview of disease epidemiology', information on sexual deviations was shortened. The important identified risk, previously 'slipped femoral epiphysis', had been renamed 'slipped **capital** femoral epiphysis'.	
4.0	02-Dec-2013	-	Merge of the existing RMPs for triptorelin into a single RMP for all indications (previously separation between the triptorelin formulation used in paraphilia and triptorelin formulations used in the other indications)

		Addition of a new important potential risk 'QT interval prolongation with the use of androgen deprivation therapy'. Following review of published evidences on the topic, a class effect related to testosterone deprivation had been suggested. No information on triptorelin effect on QT interval could be retrieved from the published literature and internal data analysis was inconclusive.	An update of the product information Warning and Interactions sections on the risk 'QT interval prolongation with the use of androgen deprivation therapy' has been submitted to the EMA in December 2013.
		In accordance with the currently approved EU SmPC and in order to present a consistent information with our business partner Ipsen Pharma, the following important identified risks common to the pharmacological class were added: Tumour flare, Hypersensitivity, Erectile dysfunction/ Impotence/ Decreased libido, Mood changes/ depression, and Slipped epiphysis following withdrawal of treatment.	-
		Revision of the wording of the risks: "*Metabolic changes (increased fat mass and insulin resistance) leading to increased cardiovascular risk and increased risk of diabetes*" and "*Patients at high risk for metabolic and cardiovascular disease should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy*" into	For ease of review the concept of metabolic changes leading to increased risk of diabetes has been split from the concept of increased cardiovascular risks. The predisposed patients and specific cautions to be considered in sub-populations are now discussed as subsections of those 2 Identified risks (diabetes and cardiovascular diseases) [refer to Section SVII.3].
		"*Metabolic changes (increased fat mass and insulin resistance) leading to an increased risk of diabetes" and "Cardiovascular diseases"*, both sections discussing the effects in pre-disposed patients.	