

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No 1901/2006, as
amended**

Triptorelin

MT/W/0001/pdWS/001

Rapporteur:	Malta
Start of the procedure (day 0):	07/07/2009
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	asrma SA See section VII Arvekap Decapeptyl Depot Gonapeptyl
INN (or common name) of the active substance(s):	Triptorelin
MAH (s):	See section VII Ferring BV Ferring (Ferring AB, Ferring Laaket Oy, Ferring AS, Ferring GmbH) Ferring Arzneimittel GmbH Ferring AS Slovak Republic FGerring SAS Ferring Legemidier Beaufort Ipsen International Ipsen NV Ipsen Pharma Ipsen E.P.E. Ipsen Pharma SA Ipsen SPA Ipsen Portugal Produtos Farmaceuticos SA Beaufour Ipsen Pharma Ipsen LTD Ipsen Pharmaceuticals LTD
Pharmaco-therapeutic group (ATC Code):	LO2AE04
Pharmaceutical form(s) and strength(s):	Powder and solvent for suspension for injection 3.75mg Powder and solvent for suspension for injection 11.25mg

INDEX

I. Executive Summary

II. Recommendation

III. Introduction

IV. Scientific Discussion

Clinical aspects – summary

Clinical studies by one MAH

Clinical studies by other MAH

Rapporteur's overall comments

V. Rapporteur's Conclusion and Recommendation

MAH's responses to raised questions

VI. Request for supplementary information

VII. List of references

VIII. List of Medicinal products and marketing authorisation holders

I. EXECUTIVE SUMMARY

Triptorelin is a gonadotropin releasing hormone agonist (GnRHa). It acts by suppressing the release of luteinising hormone (LH) and follicle stimulating hormone (FSH) by the anterior pituitary gland. Besides its adult clinical indications, triptorelin is indicated for the treatment of central precocious puberty (CPP) in children. In the clinical overview provided by the MAHs (Ferring and Ipsen) publications regarding the safety and efficacy of triptorelin since its introduction in 1986 are presented and discussed. Recommendations were made as outlined below regarding posology and method of administration, dosage, additional safety data and ADR classification were made. It was suggested that a type II variation should be made to include the recommendations to upgrade the SmPC.

II. RECOMMENDATION

In connection with Pd WS according to Article 45 of the Paediatric Regulation (EC) No 1901/2006 as amended, having assessed the paediatric data submitted by the MAHs regarding the treatment of central precocious puberty (CPP) in children treated with triptorelin, and as well as having considered the responses received from the MAHs and a comment from a Member State following the submission of a Preliminary Assessment Report, it was agreed that the following be added to the currently approved SPCs:

Section 4.2 Posology and method of administration in the first sentence states that: “The product should only be used under the supervision of an appropriate specialist having requisite facilities for regular monitoring of response.” To this statement it is agreed that the following should be added. *“The treatment of children with triptorelin should be under the overall supervision of the paediatric endocrinologist or of a paediatrician or endocrinologist with expertise in the treatment of central precocious puberty.”*

It is agreed that **section 4.4 Special warnings and precautions for use** should include the following information: *“Bone mineral density (BMD) may decrease during GnRHa therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.”*

The following information should be contained in the SPC of both MAHs:

“Slipped capital femoral epiphysis (SCFE) can be seen after withdrawal of GnRHa treatment”.

It is agreed that in **Section 4.8 Undesirable side effects of all SPCs** for triptorelin the MAHs should include **ADR frequency classification table according to the MedDRA organ system class for children** using the convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to, $1/10$); uncommon ($\geq 1/1000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1000$); very rare ($\leq 1/10,000$)

It is agreed that the general term epiphysiolysis mentioned in the SPC should be replaced by the more specific term **slipped capital femoral epiphysis (SCFE)**.

It is agreed that **next PSUR** should include **monitoring of traumatic fractures**.

It is recommended that the SPCs be updated.

IIa. Additional Recommendation following Day 90 draft Final Assessment Report:

It is recommended that the dose recommendation of the triptorelin 3.75mg for the paediatric indication be as recommended in the EU SPC as agreed to during a MRP procedure (NL/H/0263).

There is a split opinion among Member States regarding the 11.25mg dose of triptorelin. It is to be pointed out that this 11.25mg product would not be acceptable for the paediatric indication in the Netherlands.

A type II variation must be submitted by the MAHs at the end of the Paediatric Work sharing procedure.

III. INTRODUCTION

The MAHs submitted six completed paediatric studies for triptorelin in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. A short critical expert overview has also been provided.

The MAHs stated that the submitted paediatric studies do not influence the benefit risk for triptorelin and that there is no consequential regulatory action. Recommendations have been made regarding the inclusion of additional safety information and some additions to SmPC.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product.

IV. SCIENTIFIC DISCUSSION

Introduction

In the normal situation puberty follows when the hypothalamus begins to secrete periodic pulses of gonadotropin-releasing hormone (GnRH) which increase in amplitude sufficiently to act on the receptors of the anterior pituitary to release pulses of gonadotropins. These are luteinising hormone (LH) and follicle stimulating hormone (FSH) which stimulate the granulosa cells of the ovary to secrete oestrogens or the Leydig cells of the testes to secrete testosterone. The latter sex steroids bring about the physical changes of puberty viz. breast development and menstruation in girls and penile and testicular enlargement in boys. They also mediate the pubertal growth spurt.

In precocious puberty these changes appear prematurely with the inappropriate early onset of secondary sex characteristic and menstruation, behavioural and emotional changes. These changes are also accompanied by accelerated height velocity which results in a premature growth spurt associated with early epiphyseal closure and an eventual compromise of adult final height.

Puberty is considered to be precocious if changes in the secondary sexual characteristics appear before the arbitrary age of 8 years in girls and 9 years in boys. Precocious puberty which is due to early release of GnRH by the hypothalamus is termed central precocious puberty (CPP)

Human GnRH is a decapeptide that selectively stimulates the gonadotropic cells of the anterior pituitary to release the gonadotropic hormones LH and FSH. GnRH agonists (GnRHAs) have been synthesized which have an increased affinity for the GnRH receptors in the anterior pituitary and which are resistant to enzymatic degradation allowing for an increased duration of action. Triptorelin is a GnRH agonist (GnRHa) which was first synthesized by Scholly in 1971 and for which he was awarded the Nobel Prize. It differs from human GnRH in that D-tryptophane replaces glycine in position 6 of the molecule. This makes it 100 times more potent than human GnRH and has a longer half life.

If sufficient GnRHa is administered *continuously* in contradistinction to the natural *pulsatile* GnRH release by the hypothalamus, LH and FSH levels fall resulting in a fall of oestrogens and testosterone. Triptorelin and other GnRHAs initially raise the plasma LH and FSH levels and when sufficient levels of GnRHa are achieved and maintained, then LH and FSH levels fall resulting in a decrease of sex steroids. This decrease results in suppression of the rapid progress of pubertal changes and normalisation of bone growth which occurs in children with CPP.

Decapeptyl CR or Decapeptyl Depot which was used in the submitted trials is a suspension of triptorelin for injection which is encased in biodegradable polymer particles of DL- lactide-coglycolide from which it is released at suppressive concentrations over a period of 4 weeks. This is a clear advantage over the burden of the frequency of a daily injection of triptorelin. A further improvement is the Decapeptyl Sustained Release 11.25mg formulation which could be administered every 3 months resulting in less frequent injections during treatment.

At the beginning of treatment one injection with one syringe equivalent to 3.75 mg triptorelin is given, on days 0, 14, and 28. Thereafter one injection is given every 4 weeks. Should the effect be insufficient, the injections may be given every 3 weeks and then modified according to response. Dosing should be based on body weight. Children weighing less than 20 kg are injected with 1.875 mg (half dose), children between 20 and 30 kg receive 2.5 mg (2/3 dose), and children with more than 30 kg body weight are injected with 3.75 mg triptorelin (full dose).

The dose of Decapeptyl SR is 11.25mg is once every 3 months.

IV.1 Clinical aspects

1. Introduction

The MAH submitted three report(s) for Decapeptyl

SUMMARY OF CLINICAL PROGRAM SPONSORED BY ONE OF THE MAHs

Study	Design	Dosage	Evaluations
German study 1994 CT reference 34 Sippel WG et al.	A multicentre study of D-Trp6-LHRH microspheres (Decapeptyl controlled release) in treatment of true precocious puberty. This was an open, non-controlled clinical	Decapeptyl Depot 75µg/kg and up to maximum of 3.75 mg on days 0,14, 28 and then every 4 weeks	Tanner stages, height parameters, bone age hormonal suppression (LH, FSH, estradiol, testosterone)

	Phase III study carried out in Kiel and 32 other sites in Germany in 73 children with true precocious puberty to evaluate Tanner stages, height parameters, bone age hormonal suppression (LH, FSH, estradiol, testosterone) efficacy, safety and tolerability of triptorelin		
Dutch study 1994 Drop SLS et al. CT reference 35	A multicentre study of D-Trp6-LHRH microspheres (Decapeptyl CR) in the treatment of true precocious puberty. This was an open, non-controlled Phase III study carried out in Rotterdam and five other sites in the Netherlands in 39 children with central precocious puberty to evaluate the efficacy, safety and tolerability of triptorelin.	Half, two thirds or whole syringe containing 3.75mg of Decapeptyl Depot.	Tanner stages, height parameters, bone age, hormonal suppression (LH, FSH, estradiol, testosterone), prolactin, DHEAS, somatomedin-C
Israeli study 1994 Kauli Rivka CT report reference:36	A retrospective study of triptorelin CR in central precocious puberty. This was an open, non-controlled retrospective study carried out in Tel Aviv in 30 children with central precocious puberty to evaluate the efficacy of triptorelin.	Decapeptyl Depot 1.25 – 3.75mg every 4 weeks depending on body weight.	Tanner stages, height parameters, bone age hormonal suppression (LH, FSH, estradiol, testosterone), DHEAS, somatomedin-C

1. Clinical studies

CLINICAL STUDIES SUBMITTED BY ONE OF THE MAHs

1. CT reference number 34 conducted by Sippell WG et al. 1994

“A multicentre study of D-Trp6-LHRH Microspheres (Decapeptyl Contolled Release) in the treatment of true precocious puberty”.

This was an open, non-controlled Phase III study carried out in Kiel and 32 other sites in Germany in 73 children to evaluate the efficacy, safety and tolerability of triptorelin.

In addition to the above mentioned main therapeutic goals the objectives of the study were as follows:

- i. to suppress pituitary gonadotropins and particularly gonadal steroids down to pre-pubertal levels
- ii. to slow down, halt or reverse development of secondary sex characteristics and stopping of menstruation in girls
- iii. to inhibit the rapidly advancing skeletal maturation and to normalise accelerated growth velocity
- iv. thus improving predicted adult height

Assessor’s comments

This early (1985-1991) Phase III study is relatively a large one considering that the frequency of central precocious puberty (CPP) is only 1 in 5000 to 1 in 10000. In the study it was clearly shown that triptorelin was effective in significantly suppressing the pituitary gonadotrophin and plasma sex steroids to pre-pubertal levels thus arresting or reversing the secondary sex characteristics which appear inappropriately early in CPP. Even after GnRH stimulation performed at regular intervals throughout the study, LH did not rise significantly above the upper normal limit for pre-pubertal children. Triptorelin inhibited the rapid bone maturation and accelerated height velocity normalising them, improving adult height by preventing early closure of the epiphysis. This study had the advantage that the rate of bone maturation $\Delta BA/\Delta CA$ before starting therapy was assessed and therefore the normalisation of the bone maturation rate could be more clearly demonstrated.

Psychological evaluation seemed to demonstrate reduction of psychological complaints and anxieties in the children and parents but no statistical analysis of the results of this aspect of treatment of CPP with triptorelin was made. No firm conclusions about the psychological benefit of treatment could be drawn.

Apart from vaginal bleeding recorded 13 times there were no serious adverse effects.

No significant triptorelin antibodies were found in any of the 41 children tested for them.

2. CT reference number 35 conducted by Drop S.L.S. et al.

A multicentre Study of D-Trp6-LHRH Microspheres (Decapeptyl Controlled Release) in the treatment of true Precocious Puberty.

This was an open, non-controlled Phase III study carried out in Rotterdam and five other sites in the Netherlands in 39 children with precocious puberty to evaluate the efficacy, safety and tolerability of triptorelin.

In addition to the above mentioned main therapeutic goals the objectives of the study were:

- i. to suppress pituitary gonadotropins and particularly gonadal steroids down to pre-pubertal levels
- ii. to slow down, halt or reverse development of secondary sex characteristics and stopping of menstruation in girls
- iii. to inhibit the rapidly advancing skeletal maturation and to normalise accelerated growth velocity
- iv. thus improving predicted adult height

Assessor's comments

This early study (1985 to 1988) was very similar to the previous CT reference 34 study in its aims and results. The study was over a period of 104 weeks. In this study which involved 39 children during treatment with triptorelin, puberty was arrested or regressed in most patients to a lower Tanner stage.

Pituitary gonadotrophins fell markedly in the first 2 weeks and plasma sex steroids remained well suppressed during treatment.

The mean $\Delta\text{BA}/\Delta\text{CA}$ ratio decreased as did also the growth velocity. Ultrasound showed a reduction of the size of the ovaries and uterus. The results of this study are similar to the results of the previous study showing that during the period of treatment triptorelin is effective in suppressing puberty and linear growth with increase of the predicted adult height.

A psychological questionnaire was administered but results were difficult to interpret because of missing data. Although an improvement was noted no firm conclusions could be drawn for this aspect of the study.

Adverse events reported included 6 girls with vaginal discharge or bleeding, local injection pain and upper respiratory infections. One girl had a serious adverse event after injection viz. fatigue and collapse which required hospital admission. She had other temporal lobe atrophy and was on epanutin. She had also proved recent parainfluenza. She responded to treatment and continued the course of triptorelin without further problems.

Clinical study reference number 36 conducted by Rivka Kauli

This was an open, non-controlled long-term retrospective prospective study of triptorelin CR in 30 children with central precocious puberty in Tel-Aviv. The objective of the study was to evaluate the

efficacy of triptorelin over several years of therapy. This ranged from 2.1 to 6.9 years after the first injection.

Assessor's comments

This early (1985-1992) Phase III retrospective clinical study includes patients who had a long period of treatment up to 7 years and focuses on control of pubertal development and measurable parameters so that it could be compared to similar European studies with triptorelin used to treat CPP.

Breast development was arrested or regressed. During treatment the bone maturation ratio $\Delta BA/\Delta CA$ from 1.37 to 0.5. Basal pituitary gonadotrophins and LH response to standard GnRH stimulation test and sex steroids were decreased to pre-pubertal levels.

There were no serious side effects which required hospitalisation. Vaginal bleeding occurred in 9 girls and this was attributed to withdrawal bleeding after stopping cyproterone therapy. In one girl this was attributed to re-starting therapy with triptorelin after stopping it. The paucity of reported adverse events in the study may be due to the fact that this was a retrospective study.

Overall assessor's comments

The three studies submitted by one of the MAHs for PdWS were published in 1994. The first two studies are similar prospective studies. All three studies clearly showed the efficacy of Decapeptyl Depot injection in suppressing the early development of puberty. The German study has the advantage that the rate of bone maturation ($\Delta BA/\Delta CA$) was assessed before therapy so that the decrease in maturation during treatment could be clearly demonstrated.

With regard to early safety data from these studies it results that there were no deaths during the trials. One serious adverse event reported in the Dutch study concerned a girl who had to be hospitalised because of collapse and fatigue after injection. However, she responded to treatment. It was established that she had atrophy of the temporal lobe and was on phenytoin therapy. She also had proved recent parainfluenza. She continued with Decapeptyl Depot treatment without further problems.

As is usual in children the most common adverse events were upper respiratory tract infections but the rate was not higher than in children in the general population. More likely to be related to the treatment were the occurrence of vaginal haemorrhage or spotting and vaginal discharge which occurred during the first two to three months of treatment. Other less frequent adverse events reported were itching, erythema, stomach pain and severe pain at the site of injection.

Apart from this early information which resulted from these studies Saggese et al. 1993 (1), they found that during the treatment with Decapeptyl Depot bone mineral density decreased significantly at 6 months to: - 6,0%, $p < 0.002$ vs. baseline and at 12 months : - 8.0%, $p < 0.001$ vs. baseline.

In the Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children 2009 (2) it was stated that although BMD may decrease during GnRHa therapy subsequent bone mass accrual is preserved and peak bone mass does not seem to be negatively affected.

It is felt that although ultimately the outcome regarding BMD after cessation of GnRHa is favourable by the end of adolescence according to Heger S et al. 1999 (3) and van der Sluis et al. 2002 (4), a fundamental change occurs temporarily in the patient's bone metabolism during treatment with triptorelin and as such it deserves to be mentioned in Section 4.4 of the SPC. Apart from the need for increased awareness of the change in BMD there may be the remote possibility of increased liability to traumatic fractures in heavy children. Advice about optimum supplements of calcium and exercise may help to attain an optimal peak bone mass may be appropriate as suggested by Antoniazzi F et al 2003 (5). This may be very important in girls with regard to the degree of possible post-menopausal osteoporosis. Decrease in BMD is important and its possible occurrence should be mentioned.

In section 4.4 of the SPC under women it is stated that treatment with Decapeptyl Depot over several months can lead to a decrease in bone density. In children triptorelin is used for several years rather than months and users should be aware of the possibility of decrease in mineral bone density in children during prolonged treatment. At centres of excellence mineral bone density is indeed measured at the end of GnRHa therapy and at intervals until adulthood.

It is recommended that **section 4.4 Special warnings and precautions for use** should include the following information: *“Bone mineral density (BMD) may decrease during GnRHa therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved, and peak bone mass in late adolescence does not seem to be affected by treatment. Slipped capital femoral epiphysis can be seen after withdrawal of GnRH treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.”*

SUMMARY OF CLINICAL PROGRAM SPONSORED BY ANOTHER MAH

Study	Design	Dosage	Evaluations
Study 914CL 20E By Prof. Pierre Canlorbe	An open clinical non comparative study and laboratory evaluation carried out in 27 children with true precocious puberty (due to hypophyseal gonadotrophin hyperactivity)treated wit D-TRP-6-LHRH Intramuscular microcapsules	D-TRP-6-LHRH (Decapeptyl-microcapsules) Children < 20kg = 1mg Children 20 -30kg = 1.5mg Children > 30kg = 3mg	Slowing of the rate of statural growth and bone maturation (Greulich & Pyle). Regression of sexual maturation (Tanner), volume of gonads ultrasonography in girls. Assay of plasma testosterone/estradiol IV LHRH test Side effects Acceptability

<p>CT reference 914 Cl 461R By Chaussain J.L. 1994 Synopsis only provided in English</p>	<p>A multicentre clinical study of Decapeptyl SR microspheres in the treatment of precocious puberty. Thus was a multicentre open label non-comparative clinical trial carried out in 81 children Phase II – III to evaluate the effects of Decapeptyl SR on auxiological and hormonal parameters and on pubertal development in children with precocious puberty</p>	<p>Decapeptyl SR 3.75mg injection every 4 weeks. Children < 30kg body weight received one third or half of a syringe, Patients > 30kg received a full syringe.</p>	<p>Bone age, height age, height, height SDS, target height, growth velocity, height age to bone age ratio, pubertal development Tanner, Hormonal parameters: Basal and LHRH- stimulated plasma LH and FSH, estradiol and testosterone.</p>
<p>Study report E28 52014 708 Prof J.C. Carel 2004</p>	<p>A Phase III, multicentre, non comparative, one single group, open study to assess the efficacy and tolerability of triptorelin 11.25 mg in 64 children over 20 kg. with precocious puberty. The trial was carried out in 15 centres in France, Belgium, Spain and Italy.</p>	<p>Triptorelin P.R. 11.25mg: triptorelin (INN) acetate sustained release formulation over 3 months</p>	<p>Pubertal staging, uterine length LH and FSH response to LHRH test. Suppression of LH, estradiol or testosterone. Auxiological parameters: height, height SD score, PAH, growth velocity, bone age variation, Residual triptorelin in plasma. Adverse events, physical examination. Biochemistry parameters</p>

Study 914Cl 20E

Study of D-TRP-6-LHRH in the Form of Intramuscular Microcapsules in the Treatment of Precocious Puberty

This was an open clinical non comparative study and laboratory evaluation carried out in 27 children with true precocious puberty treated with D-TRP-6-LHRH intramuscular microcapsules (Decapeptyl microcapsules). The study population was made up of 16 girls under 9 years of age and 11 boys under 11 years.

Study 914 CL 20E is an early study which clearly shows the efficacy of triptorelin 3.75 mg in the treatment of precocious puberty during the first 6 months of treatment. It demonstrates the significant reduction of basal and peak LHRH stimulated gonadotrophins LH and FSH and of plasma estradiol or testosterone. Puberty was suppressed with arrest or regression of genital development to a lower stage. Growth velocity was reduced to pre-pubertal rates. Time was insufficient to calculate $\Delta BA/\Delta CA$ to show reduction in bone maturation but calculation in months using statural age/bone age $\Delta SA/\Delta BA$ was >1 showed that there was a significant decrease in bone maturation.

With regard to safety adverse events reported were minor and included small genital haemorrhages 9 days following the first injection (n=5) and second injection (n=2), transient rash(n=1), behavioural disorder (n=1) and pain on injection (n=2)

Study 914Cl 461R

Essai Clinique Multicentrique du Decapeptyl 3.75mg dans les Pubertés Précoces

This was a multicentre clinical study of Decapeptyl microspheres in the treatment of precocious puberty.

This was open label non comparative study carried out in 81 children (71 girls and 10 boys) Phase II – III to evaluate the effects of Decapeptyl SR on auxiological and hormonal parameters and on pubertal development during and after therapy in children with central precocious puberty.

Study 914 CL 461R is a later study 1991/1994. Only the synopsis was submitted in English. It concerns the treatment of central precocious puberty with Decapeptyl SR administered IM every 28 days. It is an interesting study because besides being of considerably longer duration viz. 3.5 ± 1.5 years in girls and 4.0 ± 2.2 in boys it also provides data not only during treatment but also after its cessation.

Assessor's comments

The results obtained during treatment are similar to those of other studies in which CPP was treated with Decapeptyl SR 3.75 mg. During treatment the mean plasma basal levels and mean stimulated LHRH peaks of LH and FSH and of the mean plasma levels of estradiol and testosterone were significantly decreased. After cessation of therapy the levels of these hormonal parameters increased significantly above pre-pubertal values showing reversibility on cessation

During treatment menstruation ceased if menarche had already been achieved. Pubertal development was either arrested, slowed down or had regressed. After cessation there was a resumption of pubertal development. Menarche or re-menarche occurred 1.2 ± 0.5 years after discontinuation. This showed the reversibility of pituitary - gonadal inhibition.

During treatment the bone maturation rate decreased significantly as shown by decrease in BA/CA ratio and increase in HA/BA ratio which approached the normal ratio of 1 both in girls as well as in boys. The mean growth velocity decreased significantly to below pre-pubertal rates. After discontinuation of therapy the main gain in height was + 25 cm in girls and + 27 cm in boys.

There was no information about further maturation of bone after discontinuation. With regard to safety no serious adverse event was reported arising out of the study.

Study E28 52014 708

A Phase III, multicentre, non-comparative, one single group, open study to assess the efficacy and tolerability of triptorelin 11.25mg in children with precocious puberty.

This study was carried under the coordination of Prof. JC Carel in 15 centres in France, Belgium, Spain and Italy in 64 children (54 girls and 10 boys). The study product was Triptorelin P.R. 11.25mg triptorelin (INN) acetate sustained release formulation over 3 months. The injection was administered every 3 months during 12months.

Study E28 52014 708 is a more recent (2004) study regarding the use of the triptorelin 11.25 mg formulation administered every 3 months in children with CPP.

The primary objective of the study was to assess the efficacy of suppression of triptorelin 11.25 mg at the end of 3 months (M3) with respect to the proportion of children with suppressed luteinizing hormone (LH) response to an LHRH test (LH peak ≤ 3 IU/L). Using the MNR statistical approach this was achieved in 83% of the children (83% for girls, 80% for boys).

Continued suppression response of LH to LHRH test was shown as part of the secondary criteria at M6 was achieved in 94% (94% for girls and 90% for boys and at M12 it was achieved for 88% (91% for girls and 70% for boys).

Other hormonal parameters used as secondary criteria viz. mean peak LH, mean FSH level, mean estradiol and testosterone levels measured at baseline and at M3, M6 and at M12 were significantly reduced.

Auxiological parameters at M6 and at M12 showed decrease of growth velocity and stabilization of height and bone maturation.

Puberty development regressed in 69% of the girls and a similar trend was observed in boys.

Residual triptorelin levels at M3, M6 and M12 were adequate in a large proportion of patients.

Assessor's comments

These pharmacodynamic results suggest that the triptorelin 11.25mg 3month formulation is as effective as the triptorelin 1month for the suppression of precocious puberty.

The data concerning the pharmacodynamics of repeated dosing in children with CPP with the 11.25 mg 3monthly dose are limited. Further data submitted by the MAH is a non-comparative study so that no comparative assessment of the benefit/risk ratio can be made with regard to the 11.25mg dose and the triptorelin 3.75mg monthly dose. However, the above mentioned findings of study E28 52014 708 showed that there is acceptable efficacy.

Also with regard to safety no patient withdrew from the study. Out of 64 patients 31 presented with a treatment emergent adverse event. Of these 17 were judged to be related to the treatment, headache and upper respiratory tract infections were common. Expected adverse reactions viz. withdrawal bleeding and local reactions were reported in 14% of patients.

The triptorelin 11.25mg three monthly formulation was shown to have a sustained effect and that it would result in having to administer less frequent injections for the treatment of central precocious puberty.

Assessor's Overall comment

The three studies submitted by MAH 1 in connection with PdWS according to Article 45 of the Paediatric Regulation 1901/2006 comprise two early studies concerning triptorelin 3.75mg administered IM every 4 weeks and a later study (2004) concerning the 11.25mg formulation which is administered IM every 3 months.

The data concerning the pharmacodynamics of repeated dosing in children with CPP with the 11.25 mg 3monthly dose are limited. Further data submitted by the MAH is a non-comparative study so that no comparative assessment of the benefit/risk ratio can be made with regard to the 11.25mg dose and the triptorelin 3.75mg monthly dose. However, the above mentioned findings of study E28 52014 708 showed that there is acceptable efficacy.

All three studies clearly show efficacy in suppression of gonadotrophins and sex steroids and consequently of arrest or regression secondary sex characteristics with normalization of bone maturation and linear growth. In study E28 52014 708 the primary aim was achieved viz. that there was efficacy of suppression at the end of 3 months with respect to the proportion of children with suppressed LH response to an LHRH test $LH \leq 3$ IU/L. Continued adequate suppression in this respect was also shown at the end of M6 and at M12 together with suppression of other hormonal parameters compared to baseline in children with precocious puberty

In the two early studies adverse events reported were minor viz small genital haemorrhages, transient rash and local pain. In study E28 52014 706 the intensity of the adverse reactions was mostly moderate. Apart from expected reactions viz. withdrawal bleeding and local pain, upper respiratory infections and headache were common. Three had severe reactions which included acute appendicitis, severe local pain, one patient had malaise and emotional instability.

Saggese et al. in 1993 found that during the treatment with Decapeptyl Depot bone mineral density (BMD) in children decreased significantly at 6 months to: -6%, $p < .002$ vs baseline and at 12 months: -8%, $p < 0.001$ vs. baseline.

In the Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children 2009 it was stated that although BMD may decrease during GnRH therapy subsequent bone mass accrual is preserved and peak bone mass does not seem to be negatively affected.

Although ultimately the outcome regarding BMD after cessation of GnRH is favourable by the end of adolescence, GnRHa therapy goes on for years during which a fundamental change occurs albeit temporarily in the child's bone metabolism during treatment with triptorelin and as such, by today's standards it deserves to be mentioned in Sections 4.4 of the SPCs. Apart for the need for awareness of the temporary change in BMD there may be the remote possibility of increased liability to traumatic fractures in heavy children. In order to attain an optimum peak bone mass advice about supplements of and calcium may be appropriate as suggested by Antoniazzi et al. 2003. This may be very important especially for girls with the long-term view to lessen the degree of eventual post-menopausal osteoporosis which they may eventually develop. In section 4.4 of the SPC under the indications for women it is stated that treatment with triptorelin over several months can lead to a decrease in bone density. In children triptorelin is used for several years rather than months and users should be aware of the possibility of the temporary decrease in BMD which occurs during the prolonged treatment with triptorelin. At centres of excellence BMD is measured at the end of GnRHa therapy and at intervals until adulthood.

It is recommended that **section 4.4 Special warnings and precautions for use** should include the following information: *“Bone mineral density (BMD) may decrease during GnRHa therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved, and peak bone mass in late adolescence does not seem to be affected by treatment.*

Slipped capital femoral epiphysis can be seen after withdrawal of GnRH treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.”

2. Discussion on clinical aspects

V. RAPPORTEUR'S CONCLUSION AND RECOMMENDATIONS

The above mentioned study reports regarding the use of triptorelin in the treatment of children with central precocious puberty which were submitted by the MAHs for work-sharing according to Article 45 of the Regulation 1901/2006 as amended were reviewed in terms of efficacy and safety and updating of the SPC.

Comments regarding Efficacy

The studies submitted have shown clearly that triptorelin when used in the paediatric indication of central precocious puberty is effective in suppressing the pituitary gonadotrophins LH and FSH and the plasma sex steroids estradiol or testosterone thus arresting, slowing or reversing the early inappropriate development of secondary sex characteristics (including menstruation) and in slowing the accelerated rate of bone development and also in slowing the growth velocity. The latter improved the outcome for predicted adult height by delaying premature epiphyseal closure.

In the studies CT reference 34 and CT reference 35 an attempt was made to demonstrate an improvement in psychological complaints and parental anxieties associated with precocious puberty but no firm conclusions could be drawn.

Study E28 52014 706 concerned the 11.25mg triptorelin 3 monthly formulation rather than the 3.75mg monthly formulation used in the other studies. The primary aim of this study was to assess the efficacy of this formulation with respect to the proportion of children with suppressed luteinizing hormone (LH) response to a luteinizing hormone releasing hormone (LHRH) test at month 3 (LH peak \leq 3IU/L). This was achieved in 83% (83% girls, 80% boys) of the ITT population.

The results of the secondary aims of this study showed a sustained suppression at month 6 and month 12 were 94% (94%girls, 90% boys) and 88% (91% girls, 70%boys). Other hormonal parameters viz. mean peak levels of LH and FSH and mean sex steroid levels were also significantly reduced to pre-pubertal levels. A sustained effect of the 11.25mg triptorelin over a 12 month period with suppression of puberty and normalisation of acceleration of linear growth which was similar to that of the 3.75mg formulation was shown.

Comments regarding Safety

Treatment related adverse events in the above mentioned early trials with triptorelin 3.75mg injection in children with CPP were generally mild and were related to the pharmacological effects of triptorelin and included vaginal haemorrhages and/or discharge, pain at the site of injection, headaches and hot flushes. One patient who suffered collapse and fatigue required hospitalisation. However she had been on anti-epileptic treatment and had had recent proved para-influenza infection. She quickly recovered and could continue triptorelin treatment without further problems.

In the later (2004) study E28 52014 708 with the triptorelin 11.25mg formulation treatment related adverse events were generally mild and well tolerated except for two patients with serious adverse events requiring hospital admission: one had acute appendicitis, and the other had syncope. Both adverse events were believed not to be due to the investigational drug.

One of the MAHs performed a review of world-wide safety data obtained with their own triptorelin PR formulation including serious adverse events from clinical trials and post-marketing surveillance reports. The review showed that allergic reactions accounted for about 15% of all the ADRs reported in both children and adults was stable over time: 1/15000 treatment months in children with CPP.

The majority of hypersensitivity-type reactions reported since the IBD (International Birth Date) were of rash, urticaria, and oedema. These occurred irrespective of the indication for use. Most were mild non-serious and transient but 4 adverse reactions (ADRs) of anaphylactic shock and 1 anaphylactoid reaction were reported. These recovered but in one case of anaphylactic shock documentation was poor and the outcome was unknown. There have also been 20 ADRs reported for the preferred term hypersensitivity and 2 ADRs of injection site hypersensitivity, but the risk of hypersensitivity remains stable and low, with an incidence of less than 4/100,000.

Another MAH carried out post-marketing safety experience regarding the use of Decapeptyl Depot from March 1986 to 28 February 2009 does not indicate separately the number of children in whom it was used. However, up to 28 February 2009 the Global Pharmacovigilance received reports of 105 cases in patients under 18 years of age. Of these 87 were in children ≥ 2 to < 12 years and 18 were in adolescents ≥ 12 to < 18 years.

In children on an event level the most frequently affected MedDRA system organ class (SOC) were skin and subcutaneous tissue disorders (61/184). Twenty - five cases were serious. Of these 10 were unlisted and included 2 cases of epiphysiolysis, one case of allergic bronchospasm with facial oedema and synovitis.

In the adolescent group the most frequently affected SOC were general disorders and injection site conditions (8/35) followed by skin and subcutaneous tissue disorders (7/35). Among the adolescents out of 4 unlisted serious ADRs, 2 were due to epiphysiolysis. This makes a total of 4 cases of epiphysiolysis, 2 in children under 12 years and another two in adolescents and this happened in a relatively small population.

In the various safety reports there is no generally agreed convention regarding the grouping of allergic reactions following the injection of triptorelin viz. rash, oedema, urticaria, wheezing, hypersensitivity, anaphylactic and anaphylactoid reactions all of which may have a common underlying pathology of allergy. It would appear that using names of different allergic manifestations tends to dilute the number of allergic/hypersensitivity reactions in a small population this makes comparisons difficult. There is a need to harmonise the reporting of such reactions.

The cause of epiphysiolysis or slipped capital femoral epiphysis (SCFE) is not known but it is associated with obesity. It frequently manifests itself more often in males than in females during the paediatric growth spurt. The annual incidence of SCFE for the general population, according to Nelson Textbook of Pediatrics 18th Edition is 2 per 100,000 in the general population. Incidence varies from 0.2 per 100,000 in Japan to 10.08 per 100,000 in the north eastern United States. Overweight and the suppression of estradiol during treatment of CPP with GnRHAs may be possible contributory factors for the development of epiphysiolysis involving the femur. In the interest of clarity it is recommended that the more specific term indicating the site of anatomy involved be used in the SPC viz. **slipped capital femoral epiphysis (SCFE)** be used rather than the generic term epiphysiolysis. This may be important for the patient if it is so mentioned in the package leaflet (PIL) as it may happen in

adolescence when the patient may no longer under close medical supervision after cessation of GnRHa therapy.

General Comments

Section 4.2 of the SPC states that “The product should only be used under the supervision of an appropriate specialist having the requisite facilities for regular monitoring of response.”

Some adult endocrinologists and some specialist paediatricians other than paediatric endocrinologists might consider treating central precocious puberty with GnRH analogues. Further in some countries treatment is carried out on a shared basis between the paediatric endocrinologist, the general paediatrician or even the family physician. During the treatment, precocious pubertal development is suppressed or may be insufficiently suppressed needing adjustment. Growth has to be closely monitored as it may be unduly slowed down again requiring endocrinological intervention. It is important that it should be emphasized that GnRHa treatment should be under the overall supervision of the paediatric endocrinologist so that auxiological and hormonal measurements, skeletal studies, follow-up post treatment and their documentation can be appropriately carried out. This is a very delicate and complex period in the development of the child. There must be a clear delineation of responsibilities. For this reason it is recommended that to the statement ”The product should only be used under the supervision of an appropriate specialist having the requisite facilities for regular monitoring of response” the following statement should be added **“The treatment of central precocious puberty should be under the overall supervision of a paediatric endocrinologist.”**

In Section 4.4 Special warnings and precautions for use under Women states that treatment with Decapeptyl Depot over several months can lead to decrease of bone density which is generally reversible 6 to 9 months after withdrawal of treatment. In children the product is used rather for several years and considering its action in normalising bone age there is no reason to believe that a similar decrease in mineral bone density does not occur also in children.

In the Consensus Statement on the Use of Gonadotropin –Releasing Hormone Analogs in Children reported in *Pediatrics* 2009 it is mentioned that bone mineral density (BMD) may decrease during GnRHa therapy. However, subsequent bone mass accrual is preserved and peak bone mass does not seem to be affected by treatment. It would appear that ultimately by late adolescence the bone mineral density comes within the normal range for age. Bone mineral density loss during GnRHa therapy in children may be considerable. Saggese et al reported in the *Eur J Pediatr* 1993 (1) that the decrease after 6 months treatment with GnRHa was – 6% $p < 0.002$ vs. baseline and that after 12 months it was - 8% $p < 0.001$ vs. baseline. It appears that by late adolescence BMD is within the normal range for age.

Even though the situation normalises after cessation of therapy a profound change in bone mineral metabolism occurs during the treatment of children with GNRHas. All professionals and the carers of the child should be accordingly informed of the pharmacodynamics of the treatment drug viz. the mineral bone density loss during the period of treatment with triptorelin. With rapid mineral bone density loss here is the remote possibility of traumatic fracture especially in heavy children during violent sport. Although the attainment of optimal peak bone mass depends on many different factors there is also the option of considering the use calcium supplements as part of the treatment as suggested by Antoniazzi F et al 2003. This may be important with regard to the degree of eventual menopausal osteoporosis which the individual might eventually develop. In centres of excellence children who have received GnRHa therapy have their mineral bone density measured at the end of treatment and at intervals thereafter until adulthood.

It is therefore recommended that **section 4.4 Special warnings and precautions for use** should include the following information: *“Bone mineral density (BMD) may decrease during GnRH α therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved, and peak bone mass in late adolescence does not seem to be affected by treatment. Slipped capital femoral epiphysis can be seen after withdrawal of GnRH treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.”*

Not all current SPCs regarding triptorelin contain up-to-date information regarding undesirable effects when used for the indication central precocious puberty. It is recommended that in **Section 4.8 Undesirable side effects of all SPCs** for triptorelin the MAHs are requested to include **ADR frequency classification table according to the MedDRA system organ class for children** using the convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $1/10$)); uncommon ($\geq 1/1000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1000$); very rare ($\leq 1/10,000$)

**MAH's Responses to raised questions concerning Post-Approval Safety Monitoring
Rapporteur's comments for triptorelin following Recommendations in the Preliminary
Assessment Report in the EMEA Paediatric Worksharing Procedure (MT/W/0001/pdWS/001)**

1) SPC, section 4.2 Posology and method of administration

Following questions raised in the PAR in the EMA Paediatric Worksharing procedure MT/W/0001/pdWS/001 it was recommended that the SPC *section 4.2 Posology and Method of Administration* should include the wording “The treatment of children with triptorelin should be under the overall supervision of a paediatric endocrinologist or of a paediatrician or endocrinologist with expertise in the treatment of Central Precocious Puberty”.

2) SPC, section 4.4 Special warnings and precautions for use

It was also recommended that the SPC *section 4.4 General warnings and precautions for use* should contain the wording that “Bone mineral density may decrease during GnRH therapy for Central Precocious Puberty (CPP). However, after cessation subsequent bone mass in late adolescence does not seem to be affected by treatment” and a second statement to be included is “Slipped capital femoral epiphysis (SCFE) can be seen after withdrawal of GnRHa treatment”.

3) SPC, section 4.8 Undesirable side effects

The MAHs agreed that the ADR frequency classification table according to the MedDRA organ system class for children in the SPCs should be updated. The last column “Additional rare post marketing AEs” will be replaced by heading “Additional post-marketing AEs, frequency not known, cannot be estimated from available data.”

System Organ Class	Very Common AEs	Common AEs	Additional rare post-marketing AEs
	≥ 10%	≥1% - <10%	≥0.01% - <0.1%
Gastrointestinal disorders			Vomiting Abdominal pain Abdominal discomfort
General disorders and administration site conditions		Pain Erythema Injection site erythema Injection site inflammation Injection site pain	Malaise
Investigations			Blood pressure increased Weight increased
Musculoskeletal and connective tissue disorders			Myalgia
Nervous system disorders		Headache	
Psychiatric disorders			Affect lability Nervousness
Reproductive system and breast disorders		Genital haemorrhage Vaginal bleeding	
Vascular disorders		Hot flush	
Respiratory, thoracic and mediastinal disorders			Epistaxis
Eye disorders			Vision blurred Visual disturbance
Skin and subcutaneous tissue disorders			Angioneurotic oedema Rash Urticaria
Immune system disorders		Hypersensitivity reaction	Hypersensitivity reaction

4) SPC terminology

Where the generic term “epiphysiolysis” is used in the SPC it should be replaced by the more specific term “Slipped capital Femoral Epiphysis (SCFE)”. It was recommended that the next PSUR includes monitoring of traumatic fractures.

5) Frequency of epiphysiolysis

In answer to the question raised by the Rapporteur whether frequency of epiphysiolysis / Slipped capital femoral epiphysis (SCFE) is higher than in children treated with GnRHs than in the general population it was stated that there is very limited data regarding the risk of SCFE in the general population and in children suffering from CPP and it is therefore difficult to separate the risk caused by CPP-induced hormonal imbalances from that which may result from the GnRH treatment.

6) Recommendation that the SPCs be updated.

The following proposals for harmonisation and updating of the SPCs at the end of the PdWS procedure via a variation procedure were accepted.

With reference to the posology:

1. for the 1 month formulation “children weighing >20kg: one I.M. injection every 28 days. Children weighing <20kg: half dose of triptorelin 3.75mg that is, half the volume.”
2. for the 3 month formulation “One intramuscular injection every 3 months”.

With reference to the age of the boy: “before 10 years in boys” should be included as already approved in a Member State.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

With regard to Triptorelin 11.25mg, comments have been received from a Member State that: “In the absence of insufficient clinical data, the benefit-risk for Triptorelin 11.25mg in children with a body weight of above 20kg cannot be adequately assessed and is therefore not acceptable.” Further concern is raised that “Triptorelin 11.25mg dose is known to result in more profound suppression of the GnRH release in comparison to the suppression noted with the 3.75mg dose.”
The applicant is requested to comment on the above statements.

Response:

REQUEST FOR SUPPLEMENTARY INFORMATION

Statement 1: With regard to Triptorelin 11.25mg, comments have been received from a Member State that: “In the absence of insufficient clinical data, the benefit-risk for Triptorelin 11.25mg in children with a body weight of above 20kg cannot be adequately assessed and is therefore not acceptable.”

MAH Response

The MAH has asked the assessor for clarification of this statement. The assessor has answered by email on 20 Oct that the MS comment is: *‘In the absence of insufficient clinical data, the benefit-risk for Triptorelin 11.25mg in children with a body weight of above 20kg cannot be adequately assessed and is therefore not acceptable.*

As detailed in the submitted documentation, a Phase III, multicentre, non-comparative, open study has been performed to assess the efficacy and tolerability of triptorelin 11.25 mg in children with precocious puberty (Study number E-28-52014708). This study was carried out in 15 centres in France, Belgium, Spain and Italy in 64 children (54 girls and 10 boys). The injection was administered every 3 months over 12 month. This study has supported the registration of this formulation in 8 EU countries. In the protocol, weight ≥ 20 kg is one of the pre-inclusion criteria. At the time of national marketing approvals in EU, the 3 month formulation was registered for children without a weight adjustment, except in Greece.

The 11.25 mg dosage will allow delivery of triptorelin over 3 months regardless of the weight of the children: there is no cumulative effect, and no over dosage described. The treatment objective is to overcome the threshold of pharmacodynamic effect. On review of the MAH 1 safety database, the safety profile observed with the 3 month formulation is consistent with that in children treated with 1 month formulation since 1986 (see response to Statement 2 below).

The MAH takes the opportunity to this question to notify a mistake in the last sentence of the section IV Scientific discussion of the Preliminary Assessment Report, it is mentioned ,...’ *the Decapeptyl SR*

11.25 mg is used in children over 20 kg'. This statement is not in accordance with the approved posology in EU countries, except in Greece.

The Rapporteur erroneously assumed that it was not to be used in children under 20 kg but it was later clarified in the response to the additional question that this was only a pre-condition for inclusion in the study. Please refer below.

Statement 2: “Triptorelin 11.25mg dose is known to result in more profound suppression of the GnRH release in comparison to the suppression noted with the 3.75mg dose.”

MAH response

Triptorelin 11.25 mg dose results in triptorelin release in a more sustained manner than 3.75 mg formulation : release during a 3 months period versus a 1 month period. Triptorelin 11.25 mg consists of microparticles of triptorelin dispersed in a matrix of copolymers of D, L-lactic and glycolic acids. There are three different types of microparticles: one releasing active ingredient during the first month, one during the second month and one during the third month.

Between the two formulations, only the duration of the hormone blockage differs: a pharmacodynamic equivalence of one single injection of triptorelin 3-month formulation with 3-monthly injection of triptorelin 1-month formulation has been demonstrated in 3 different studies already submitted in EU countries where Decapeptyl is marketed. The effect of triptorelin 11.25 mg is comparable to those of triptorelin 3.75 mg with regard to achievement of castration and pituitary desensitization: the curves representing the testosterone, estradiol or LH plasma levels for the two treatments (3-month and 1-month) are superimposable, showing a very strong pharmacodynamic similarity between both formulations (Teillac et al, 2004)¹. In addition, the study conducted by Bertelloni et al (2007)² in 35 girls with central precocious puberty, showed statistically significant LH, FSH and estradiol reduction at 3 and 6 months compared to baseline. There were no differences between the treatment groups indicating that 3 month formulation is equally as effective as the 1 month formulation.

Figure 1: Hormonal Plasma levels over time after administration of 1 and 3 month formulations (source Teillac et al, 2004¹)

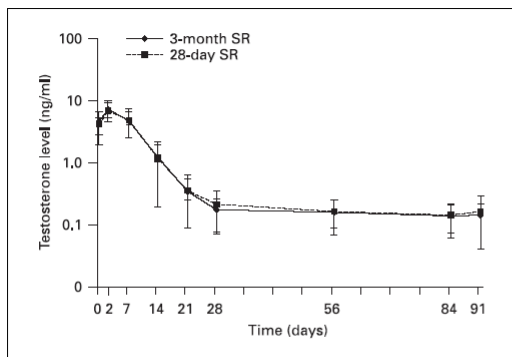


Fig. 2. Testosterone plasma levels over time (mean and SD).

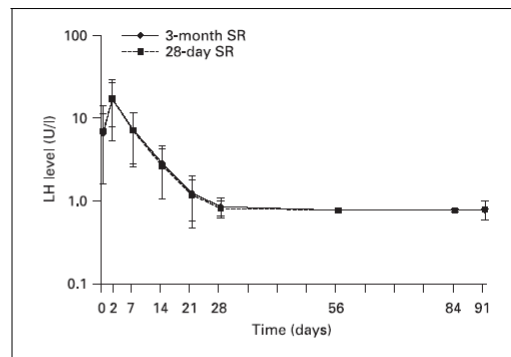


Fig. 3. LH plasma levels (mean and SD).

¹ Teillac P et al, Horm Res, 62 252-258 (2004)

² Bertelloni S et al, J Pediatric Endocrinol Metabol, 20 297-305 (2007)

This question of dosage was raised initially by the Ethics Committee at the time of the clinical study protocol submission. The MAH provided the reasons to support this regimen and the Ethics Committee accepted this rationale.

The reasons provided to support the regimen used during clinical study and proposed in the SPC are:

- there is no cumulative effect, and no over dosage described
- the treatment objective is to overcome the threshold of pharmacodynamic effect
- it has been considered as non ethical to test a lower dose with a risk of insufficient hormonal control

Triptorelin 3.75 mg was launched in 1986 for the treatment of precocious puberty and long term efficacy and post marketing safety data available in children confirmed the good safety profile found during studies. Triptorelin 11.25 mg has been marketed in adult indications since 1996 and has shown a similar safety profile as the 1-month formulation. There are no cumulative effects and the majority of adverse effects are linked to the pharmacological effects.

The advantages of the 3-month formulation is to improve the treatment compliance by decreasing the frequency of injections and to reduce the number of injections, without safety concerns. This more sustained release formulation is a great advantage for quality of life in young patients.

It is agreed that the data concerning the pharmacodynamics of repeated dosing in children with CPP with the 11.25mg 3 monthly dose are limited and that no comparative assessment can be made with the 3.75mg monthly dose. However, study E28 52014 708 showed acceptable efficiency. Treatment related adverse events were generally mild and well tolerated. The MAH's explanation with regard to the two above mentioned statements are acceptable.

VII References

Ünal et al. Effects on Bone Mineral Density of Gonadotropin Releasing Hormone Analogs Used in the Treatment of Central Precocious Puberty. J Pediatr Endocrinol Metab 2003; 16: 407-411.

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