## 13

CLINICAL PROFILE OF A NEW PURE ANTIANDROGEN (CASODEX ® ICI).

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Recently a new non steroidal or pure antiandrogen (Casodex ) has been shown in animal experience to produce a potent peripheral antiandrogen effect without activating the hypothalamic-pituitary-gonadal axis(Furr et al.1987). Clinical results in patients with advanced prostatic cancer (PCA)however proved that this compound is non selectively peripherally active and also blocks central brain androgen receptors with a subsequent rise of LH and T. Casodex, 50 mg daily was given to18 patients with PCA (T3,T4 M+) with good prognostic factors for a mean period of 42 weeks (8-80 w). Clinical, biological and endocrine parameters and side- effects were recorded on days 0,28,56,84.... There were no complete objective responses. Partial response was seen in a few patients. Prostatic volume reduction of more than 50 % occurred in 9 out of 18 patients. PAP normalized in 4 out of 9 evaluable patients while PSA diminutions of more than 50 % were seen in 16 of the 18. Subjective improvement was reported in all patients who had initial complaints. Endocrine monitoring showed a concomitant increase of LH, T and Oestradiol in almost all patients, with peak values after a period of 24 to 30 weeks. In about half of patients there was a subsequent return to lower values after this period. The most commonly reported side-effect : gynecomastia mostly mild to moderate, was noted in 15 of the 18 patients. Six patients went off study, 5 because of progression and one because of toxicity. General tolerance was good. There were no signs of liver toxicity.

We conclude that this drug's effects are similar to those of other non steroidal compounds.

## 14

PHARMACOKINETICS AND ENDOCRINE EFFECTS OF SLOW RELEASE FORMULATIONS OF LHRH ANALOGUES

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The LHRH agonists are antigonadotropic agents for reversible ovarian suppression in gynaecology and in oncology. In oncology, pituitary inhibition is maintained with high release rates preferably by implant or microcapsule injections. We have investigated the pharmacokinetics of buserelin after injection, infusion, and during implant treatment (controlled release). The release rate is monitored by urinary buserelin excretion (fractional excretion of 30 % of the daily dose). During therapy, the LHRH agonists in serum are measured by specific radioimmunoassays, with or without extraction. A convenient non-invasive procedure is to measure the amount of buserelin in 24 h urine samples (during injections or nasal spray), or the urinary buserelin/creatinine ratio in morning urine samples (during infusions or implants). After high dose injection, buserelin has a halflife of 80 min, therapeutic plasma concentrations are maintained for 8-12 hours. In long-term maintenance with buserelin implants, plasma concentrations and urinary excretion were reproducible and consistent indicating a suitable dose interval of 2-3 months. In endometriosis and mammary carcinoma, the minimum release rate (urinary buserelin) required for maintenance of steroid suppression was established (buserelin excretion of about 0.5 ug/g creatinine). Buserelin implants in prostate carcinoma are effective for 2-3 months, after a single dose of 6.6-10 mg buserelin. A consistent suppression of serum testosterone secretion was confirmed for more than two years. Microparticles are effective in rhesus monkeys. During this period, follicular maturation is completely suppressed for about 4 weeks after a single dose of 3.6 mg buserelin.

## 15

A NEW LONG ACTING LHRH DEPOT PREPARATION: FIRST ENDOCRINOLOGIC AND PHARMACOKINETIC RESULTS.

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**Introduction:** LHRH analogues are a well recognized therapeutic approach for the manipulation of metastatic prostate cancer. The development of a long acting depot is wanted for facilitating and/or improving patients compliance. The presented study is of a endocrinologic and pharmacokinetic design and concerns a new long acting biodegradable depot preparation of a LHRH analogue Zoladex (ICI 118630) 10.8 mg.

**Material and Method:** Thirty-eight patients with histologically proven locally advanced or metastatic prostate cancer were entered in the study. All patients are virgin and received once a long acting depot formulation of Zoladex 10.8 mg whithout other concomitant hormonal therapy. Blood samples for pharmacokinetic and endocrinologic analysis were taken weekly until serum testosterone reached at least twice the upper limit of the surgically castrate range on two consecutive occasions. At this moment patient received a single injection of the 28 day depot formulation of Zoladex.

**Results:** The median testosterone value before study-entry was 12.10 nmol/l (8-25.20 nmol/l). The median LH value was 4.55 U.l (1.40-18.8 U/l) (normal values 4-14 U/l). All patients had an initial endocrinologic flare-up, with median testosterone 18.25 nmol/l (10.5- 48 nmol/l). Normal values of testosterone (10-50 nmol/l), however, were never exceeded. LH had the same pattern. Clinical flare up was observed in 10.5% of the patients, hot flushes in 26% and breast tenderness in 2.6%. All patiens reached the surgical castration level (2 nmol/l) within 3-4 weeks after an initial flare up, and maintained this level for at least 14 weeks. Pharmacokinetic data show a slow release of the active drug and only a little quantity of substance (in some patients under the detection limit: 0.076 ng/ml) is enough to maintain the testosterone under the castration level.

**Conclusions:** Zoladex long acting depot formulation is efficient in reaching castrate levels of testosterone in all patients, and this level is maintained for a period of at least 14 weeks. Signs and symptoms of hormonal deprivation and clinical flare up are similar compared to the 1-monthly depot formulation and other forms of LHRH therapy. Acceptance and compliance of the patients is 100%. This new Zoladex long acting depot formulation is an effective and an even more compliant form of endocrinological management of advanced prostate cancer.

## 16

EFFECTS OF THE NEW POTENT LHRH ANTAGONIST ANTIDE

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LH-RH antagonists with a reduced potential to release histamine might represent a useful new type of androgen deprivation to treat prostatic cancer. Therefore, the ability of the third generation antagonist antide to induce a long term chemical castration in intact adult male rats and cynomolgus monkeys was investigated. The animals were treated subcutaneously with different concentrations either once or on 5 consecutive days. The effects on serum concentration of LH (only rat) and testosterone and the effects on the weights of the testes, prostates and seminal vesicles were investigated after different periods of time. Histological evaluation of testes, pituitary and hypothalamus was also performed. In the rat a clear dose-dependent inhibitory effect on the above mentioned parameters was observed whereby long-lasting castration-like effects were achieved at concentrations between 6 (up to 8 weeks) and 15mg/kg (> 8 weeks). On the other hand, in the cynomolgus monkey prolonged inhibitory effects were only induced at 15mg/kg and the duration was only 2-3 weeks. Histologically, no signs indicative of irreversible effects were observed in either species. In conclusion: Although species differences became evident in terms of the duration of a long-lasting inhibitory effect on the male reproductive system antide exhibited such an effect in the rat and the monkey and was able to induce a chemical castration in both species. In addition, using the rat Dunning R 3327 prostatic carcinoma model 10 mg/kg antide, given subcutaneously every 6 weeks for a total period of 26 weeks, had an inhibitory effect on tumor growth identical to that of castration emphasizing the suitability of this compound for treatment of prostatic cancer.