Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Centrax 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg prazepam.

Excipient with known effect:
This medicine contains 93.73mg lactose monohydrate in each tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

The risk of dependence may increase with dose and duration of treatment; therefore, the lowest effective dose and duration should be used and the need for continued treatment reassessed frequently (see section 4.4).

Abrupt discontinuation or rapid dosage reduction of prazepam after continued use may precipitate withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue prazepam or reduce the dosage (see section 4.4).

Duration of treatment
Treatment should be as short as possible.

Posology

Anxiety:

The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall duration of treatment generally should not be more than 4-6 weeks, including a tapering off process.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise.

Adults (18 years and over):

The usual dose is 30 mg daily in single or divided doses. The dose should be adjusted within the range 10 mg to 60 mg daily in accordance with response of the patient.

The lowest dose which can control symptoms should be used. It should not be usually continued beyond four weeks.

Elderly or debilitated patients:

In elderly or debilitated patients,including those with impaired liver and/or renal function, the initial dose should be small, and increments should be made gradually, in accordance with the response of the patient, to preclude ataxia or excessive sedation. Half the normal adult dose is generally sufficient for a therapeutic response in the elderly or debilitated.

The patient should be checked regularly at the start of the treatment and then regularly thereafter, in order to decrease if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

See section 4.4.

Paediatric population:

Not recommended for use in children and adolescents under 18 years old.

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or any benzodiazepines or to any of the excipients listed in section 6.1.
Myasthenia gravis
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic insufficiency

4.4 Special warnings and precautions for use

Tolerance

Tolerance to benzodiazepines may develop from continued therapy.

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Intolerance

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Dependence

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.

Once dependence has developed, abrupt termination of treatment or rapid dosage reduction will be accompanied by withdrawal symptoms which can be life-threatening. These may consist of headaches, convulsions, tremor, abdominal and muscle cramps, vomiting, nausea, sweating, diarrhoea, loss of appetite, muscle pain, extreme anxiety, tension, insomnia, restlessness, dysphoria, dizziness, vertigo, confusion and irritability. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, involuntary movements, agitation, palpitations, tachycardia, panic attacks, hyperactive reflexes, short term memory loss, hyperthermia, delirium tremens, depression, hallucinations, mania, psychosis, seizures, and suicidality.

Rebound insomnia and anxiety
A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep

disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Drug Abuse
Drug abuse is a known risk for benzodiazepines, and patients should be monitored accordingly when receiving prazepam. Benzodiazepines may be subject to diversion. There have been reports of overdose related deaths when benzodiazepines are abused with other CNS depressants including opioids, other benzodiazepines, alcohol and/or illicit substances. These risks should be considered when prescribing or dispensing prazepam. To reduce these risks the lowest effective dose should be used, and patients should be advised on the proper storage and disposal to prevent diversion of unused drug (e.g. through friends and relatives).

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2 Posology and method of administration) and should not exceed 4-6 weeks, including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment's started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Patients taking prazepam for prolonged periods should have blood counts and liver function tests periodically

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also section 4.8).

Psychiatric and 'paradoxical' reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the drug should be discontinued.

They are more likely to occur in children and the elderly.

Specific patient groups

Benzodiazepines should not be given to children without the careful assessment of the need to do so; the duration of treatment must be kept to a minimum.
Elderly patients should be given a reduced dose (see section 4.2). A lower dose is also recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy. Due to myorelaxant effect, elderly patients are of risk of falls and consequently hip fracture – caution is advised

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended Concomitant intake with alcohol

The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Take into account Combination with CNS depressants

Benzodiazepines, including prazepam, produce additive CNS depressant effects, including respiratory depression, when co-administered with other CNS depressants such as opioids, antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines (see section 4.4).

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

CYP3A4 inhibitors may reduce the metabolism of prazepam and increase the potential for toxicity.

Oral contraceptives can increase the effects of prazepam because oral contraceptives inhibit oxidative metabolism, thereby increasing serum concentrations of concomitantly administered benzodiazepines that undergo oxidation. Patients receiving oral contraceptive therapy should be observed for evidence of increased effects of prazepam. Caution is therefore recommended when oral contraceptives are co-administered with prazepam.

Benzodiazepines should be combined cautiously with clozapine because they could cause additive CNS depressant effects. Severe confusion, hypotension and respiratory depression have occurred rarely in those patients receiving clozapine concurrently or following benzodiazepine therapy. In patients receiving concomitant clozapine, the starting doses of the benzodiazepine should be approximately one-half of the usual dose until experience with the patient has been gained.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no evidence regarding prazepam's safety in human pregnancy, nor is there evidence from animal work that it is free from hazard. Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbances in offspring exposed *in utero*.

No adequate well-controlled, studies with prazepam have been performed in pregnant women. The data concerning teratogenicity associated with benzodiazepine exposure in humans are inconsistent. There are indications from some early studies that in utero exposure may be associated with congenital malformations. Later studies have provided no clear evidence of the association of benzodiazepine use and the development of these defects. In cases where an association with benzodiazepines was found, the exposure occurred mainly during the first trimester. Chronic administration during the last trimester may be associated with intrauterine growth retardation. Use during the last trimester up to delivery is associated with neonatal complications including respiratory distress syndrome, floppy infant syndrome (hypotonia, lethargy and sucking difficulties), and withdrawal syndrome (tremors, irritability, hypertonicity, diarrhea/vomiting and vigorous sucking). If benzodiazepines are used during pregnancy, or if the patient becomes pregnant while taking benzodiazepines, the patient should be apprised of the potential hazard to the fetus.

Studies with animals have shown reproductive toxicity (see section 5.3).

Prazepam is not recommended during pregnancy and in women of childbearing potential not using contraception.

Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Breast-feeding
In view of their molecular size, prazepam and its metabolites are probably excreted in human milk, therefore Centrax should not be given to nursing mothers.

Fertility
Studies in rats have shown a decrease in fertility and mating at high doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see section 4.5).

4.8 Undesirable effects

The following side effects have been observed and reported. These findings are characteristic of benzodiazepine drugs with the following frequencies

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Very Rare < 1/10,000**	**Frequency not known (cannot be estimated from the available data)**
Psychiatric disorders		Confusion, Vivid dreams,				Numbed emotions, Reduced alertness, Drug abuse (see section 4.4), Drug dependence (see section 4.4)
Nervous system disorders	Drowsiness*	Ataxia, Dizziness, Headache, Hyperactivity (Stimulations/Excitability), Light headedness, Slurred speech, Tremor	Syncope			
Eye disorders		Blurred/ Double vision				
Cardiac disorders		Palpitations				
Gastrointestinal disorders		Dry mouth, Gastrointestinal disturbances				
Skin and subcutaneous tissue disorders		Sweating, Skin rash	Itch			Skin reactions
Musculoskeletal and connective tissue disorders		Joint pains				Muscle weakness
Renal and urinary disorders		Genitourinary complaints				
General disorders and administration		Fatigue, Weakness	Swelling of feet			Drug withdrawal syndrome (see

site conditions						section 4.4)
Investigations						Decreased blood pressure, Transient and reversible aberrations of liver function tests, Increases in body weight
Reproductive system disorders						Changes in libido

* Drowsiness during the day
Other side effects include the following:

Amnesia
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Depression
Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and 'paradoxical' reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepine or benzodiazepine-like agents. They may be quite severe with this product. They are more likely to occur in children and the elderly.

Dependence
Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4 Special warnings and precautions for use). Psychological dependence may occur. Abuse of benzodiazepines has been reported (see section 4.4 Special warnings and precautions for use).

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

4.9 Overdose

As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Following overdose with any medicinal product, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Flumazenil may be useful as an antidote. Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines, and may be used when an overdose with a benzodiazepine is known or suspected. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of

benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. Consult the complete flumazenil package insert prior to use.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA11

The pharmacological effects of prazepam are mainly due to norprazepam, to which it is converted on first pass through the liver. Therefore, the drug has clinical activity similar to other benzodiazepines. It has anxiolytic, sedative, anticonvulsant and central muscle relaxant properties.

Prazepam is a benzodiazepine derivative. Studies in normal subjects have shown that prazepam has depressant effects on the central nervous system. Benzodiazepines act at the level of the limbic, thalamic, and hypothalamic regions of the CNS and can produce any level of CNS depression required including sedation, hypnosis, skeletal muscle relaxation, and anticonvulsant activity. Recent evidence indicates that benzodiazepines exert their effects through enhancement of the gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex. GABA is an inhibitory neurotransmitter that exerts its effects at specific receptor subtypes designated GABA-A and GABA-B. GABA-A is the primary receptor subtype in the CNS and is thought to be involved in the actions of anxiolytics and sedatives.

Specific benzodiazepine (BNZ) receptor subtypes are thought to be coupled to GABA-A receptors. Three types of BNZ receptors are located in the CNS and other tissues; the BNZ_1 receptors are located in the cerebellum and cerebral cortex, the BNZ_2 receptors in the cerebral cortex and spinal cord, and the BNZ_3 receptors in peripheral tissues.Activation of the BNZ_1 receptor is thought to mediate sleep while the BNZ_2 receptor affects muscle relaxation, anticonvulsant activity, motor coordination, and memory. Benzodiazepines bind non-specifically to BNZ_1 and BNZ_2 which ultimately enhances the effects of GABA. Unlike barbiturates which augment GABA responses by increasing the length of time that chloride channels are open, benzodiazepines enhance the effects of GABA by increasing GABA affinity for the GABA receptor. Binding of GABA to the site opens the chloride channel resulting in a hyperpolarized cell membrane that prevents further excitation of the cell.

5.2 Pharmacokinetic properties

Prazepam is a long acting benzodiazepine.The mean half-life of the principal active metabolite, norprazepam, measured in subjects given 10 mg prazepam three times a day for one week was 63 (±15 SD) hours before and 70 (± 10 SD) hours after multiple dosing - a non-significant difference.Repeated dosage will lead to accumulation of drug metabolites.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility
Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Prazepam administered during pregnancy caused abortions in rabbits at >25mg/kg and death in rats and deaths and malformations in their foetuses at >1000 mg/kg. Teratogenic effects in rats and abortions in rabbits, occurred at 162-fold and 8-fold the human dose based on body surface area, respectively.

Prazepam decreased fertility in male rats at 1000mg/kg, possibly by retardation of spermatogenesis, and decreased fertility and mating was observed in female rats at > 80mg/kg.

In a prenatal and postnatal study in rats, the administration of prazepam at > 25mg/kg increased the mortality of offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Microcrystalline cellulose

Maize starch
Colloidal Anhydrous Silica
Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special storage precautions are required.

6.5 Nature and contents of container

PVC/Aluminium blister pack of 60 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2023