SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clonazepam Crescent 0.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg clonazepam Excipient(s) with known effect

Each tablet contains 123.000 mg lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White to off white circular tablets, debossed with ‘CL0.5’ on one side and breakline on other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

All clinical forms of epileptic disease and seizures in infants, children and adults, especially absence seizures (petit mal), including atypical absence; primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

4.2 Posology and method of administration

Posology

Mode of administration

Treatment should be started with low doses. The dose may be increased progressively until the maintenance dose suited to the individual patient has been found. The scored tablets facilitate the administration of lower daily doses in the initial stages of treatment.

The dosage of clonazepam must be adjusted to the needs of each individual and depends on the individual response to therapy. The maintenance dosage must be determined according to clinical response and tolerance.

The daily dose should be divided into 3 or 4 equal doses. If doses are not equally divided, the largest dose should be given before retiring. Once the maintenance dose level has been reached, the daily amount may be given in a single dose in the evening.

Simultaneous administration of more than one antiepileptic drug is a common practice in the treatment of epilepsy and may be undertaken with clonazepam. The dosage of each drug may be required to be adjusted to obtain the optimum effect. If status epilepticus occurs in a patient receiving oral clonazepam, intravenous clonazepam may still control the status. Before adding clonazepam to an existing anticonvulsant regimen, it should be considered that the use of multiple anticonvulsants may result in an increase of undesired effects.

If necessary, larger doses may be given at the discretion of the physician, up to a maximum of 20 mg daily. The maintenance dose should be attained after 2 to 4 weeks of treatment.

Adults

Initial dosage should not exceed 1 mg/day.

The maintenance dosage for adults normally falls within the range 4 to 8 mg.

Elderly

Initial dose should not exceed 0.5 mg/day. The elderly are particularly sensitive to the effects of centrally depressant drugs and may experience confusion.

Paediatric population

To ensure optimum dosage adjustment, children should be given the 0.5 mg tablets.

Initial dosage should not exceed 0.25 mg/day for infants and small children (1 to 5 years) and 0.5 mg/day for older children.

The maintenance dosage normally falls within the ranges:

Infants (0 to 1 year)	0.5 to 1 mg/day
Small children (1 to 5 years)	1 to 3 mg/day
School children (5 to 12 years)	3 to 6 mg/day

In some forms of childhood epilepsy, certain patients may cease to be adequately controlled by clonazepam. Control may be re-established by increasing the dose or interrupting treatment with clonazepam for 2 or 3 weeks. During the interruption in therapy, careful observation and other drugs may be needed.

Hepatic Impairment

Patients with severe hepatic impairment should not be treated with clonazepam (see section 4.3).

Patients with mild to moderate hepatic impairment the dose should be adjusted to individual requirements and will probably be lower.

Method of administration

For oral administration

4.3 Contraindications

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

Clonazepam must not be used in patients in a coma, or in patients known to be abusing pharmaceuticals, drugs or alcohol.

4.4 Special warnings and precautions for use

Clonazepam should be used with caution in patients with chronic pulmonary insufficiency, or with impairment of renal or hepatic function, and in the elderly or debilitated. In these cases dosage should generally be reduced.

The dosage of clonazepam must be carefully adjusted to individual requirements in patients with pre-existing disease of the respiratory system (e.g. chronic obstructive pulmonary disease) or liver and in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents (see section 4.5).

Effects on the respiratory system may be aggravated by pre-existing airways obstruction or brain damage or if other medications which depress respiration have been given. As a rule, this effect can be avoided by careful adjustment of the dose to individual requirements.

Clonazepam may be used only with particular caution in patients with spinal or cerebellar ataxia, in the event of acute intoxication with alcohol or drugs and in patients with severe liver damage (e.g. cirrhosis of the liver).

Do not interrupt treatment abruptly. As with all other antiepileptic drugs, treatment with clonazepam even if of short duration, must be withdrawn by gradually reducing the dose in view of the risk of precipitating status epilepticus. This precaution must also be taken when withdrawing another drug while the patient is still receiving clonazepam therapy.

Prolonged use of benzodiazepines may result in dependence with withdrawal symptoms on cessation of use. (See ‘Dependence’).

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Suicidal behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for clonazepam.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Patients with a history of depression and/or suicide attempts should be kept under close supervision.

Concomitant use with alcohol / CNS depressants

The concomitant use of clonazepam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of clonazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5).

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

Risk from concomitant use of opioids

Concomitant use of clonazepam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe clonazepam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Driving

Like all drugs of this type, clonazepam may, depending on dosage, administration and individual susceptibility, modify the patient’s reactions (e.g. driving ability, behaviour in traffic) (*see section 4.7*).

As a general rule, epileptic patients are not allowed to drive. Even when adequately controlled on clonazepam, it should be remembered that any increase in dosage or alteration in timings of dosage may modify patients' reactions, depending on individual susceptibility.

Dependence

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products (see section 4.8). In particular long-term or high-

dose treatment, may lead to reversible disorders such as dysarthria, reduced coordination of movements and gait disorder (ataxia), nystagmus and double vision (diplopia). Furthermore, the risk of anterograde amnesia, which may occur using benzodiazepines at therapeutic dosages, increases at higher dosages. Amnestic effects may be associated with inappropriate behaviour. With certain forms of epilepsy, an increase in the frequency of seizures (see section 4.8) during long-term treatment is possible.

The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. During long-term treatment, withdrawal symptoms may develop after a lengthy period of use, especially with high doses or if the daily dose is reduced rapidly or abruptly discontinued. The symptoms include tremor, sweating, agitation, sleep disturbances and anxiety, headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and epileptic seizures which may be associated with the underlying disease. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact or hallucinations. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should therefore be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose. The risk of withdrawal symptoms is increased when benzodiazepines are used together with day-time sedatives (crossed tolerance).

Lactose intolerance

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

Porphyria

Clonazepam is considered to be probably nonporphyrinogenic, although there is some conflicting evidence. Therefore, in patients with porphyria, clonazepam should be used with care.

Paediatric population

In infants and small children clonazepam may cause increased production of saliva and bronchial secretion. Therefore, special attention must be paid to maintaining patency of the airways.

4.5 Interaction with other medicinal products and other forms of interaction

Since alcohol can provoke epileptic seizures, irrespective of therapy, patients must under no circumstances drink alcohol while under treatment with antiepileptic drugs. In combination with clonazepam, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects (see also section 4.4).

See section 4.9 for warnings concerning other central nervous system depressants, including alcohol.

Enhanced effects on sedation, respiration and haemodynamics may occur when clonazepam is co-administered with any centrally acting depressants e.g. alcohol, and other anticonvulsant (antiepileptic) agents, anaesthetics, hypnotics, psychoactive drugs and some analgesics as well as muscle relaxants and may result in mutual potentiation of drug effects (see also section 4.9).

In combination therapy with centrally-acting medications, the dosage of each drug must be adjusted to achieve the optimum effect.

There is an increased sedative effect when clonazepam is given with tricyclic and tricyclic-related antidepressants, antihistamines (less so for non-sedating antihistamines and not usually for topically applied antihistamines), antipsychotics, baclofen, lofexidine, mirtazapine, nabilone, tizanidine.

Antiepileptic drugs

When clonazepam is used in conjunction with other antiepileptic drugs, side-effects such as sedation and apathy, and toxicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment. The combination of clonazepam and sodium valproate has, rarely, been associated with the development of absence status epilepticus. Although some patients tolerate and benefit from this combination of drugs, this potential hazard should be borne in mind when its use is considered.

The antiepileptic drugs phenytoin, phenobarbital, carbamazepine and valproate may increase the clearance of clonazepam thereby decreasing the plasma concentrations of the latter during combined treatment.

In concurrent treatment with phenytoin or primidone, a change, usually a rise, in the serum concentration of these two substances has occasionally been observed.

Clonazepam itself does not induce the enzymes responsible for its own metabolism.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as clonazepam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Hepatic enzyme inhibitors and inducers

Known inhibitors of hepatic enzymes, e.g. cimetidine, have been shown to reduce the clearance of benzodiazepines and may potentiate their action. Metabolism of clonazepam is inhibited (i.e. plasma concentration is increased) by disulfiram, fluvoxamine and ritonavir.

Known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.

The selective serotonin reuptake inhibitors sertraline and fluoxetine do not affect the pharmacokinetics of clonazepam when administered concomitantly.

Special Precautions

The plasma concentration of clonazepam is possibly reduced by theophylline.

Clonazepam may possibly antagonise effects of levodopa.

There are enhanced hypotensive and sedative effects when clonazepam is given with alpha-blockers or with moxonidine.

There is an enhanced hypotensive effect when clonazepam is given with ACE inhibitors, adrenergic neurone blockers, angiotensin-II receptor antagonists, beta-blockers, calcium channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates or nitroprusside.

4.6 Fertility, pregnancy and lactation

Pregnancy

Preclinical studies in animals have shown reproductive toxicity and from preclinical studies it cannot be excluded that clonazepam possesses the possibility of producing congenital malformations (see *section 5.3*).

From epidemiological evaluations there is evidence that anticonvulsant drugs act as teratogens. However, it is difficult to determine from published epidemiological reports which drug or combination of drugs is responsible for defects in the newborn. The possibility also exists that other factors e.g. genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects.

Clonazepam should only be administered to pregnant women if the potential benefits outweigh the risk to the foetus.

During pregnancy, clonazepam may be administered only if there is a compelling indication. Clonazepam has harmful pharmacological effects on pregnancy and the foetus/newborn child.

Administration of high doses in the last trimester of pregnancy or during labour can cause irregularities in the heart beat of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor feeding in the neonate.

Infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the post-natal period.

It should be borne in mind that both pregnancy itself and abrupt discontinuation of the medication can cause exacerbation of epilepsy.

Breast-feeding

Although clonazepam has been found to pass into the maternal milk in small amounts only, mothers undergoing treatment with this drug should not breastfeed. If there is a compelling indication for clonazepam, breastfeeding should be discontinued.

Fertility

Effects on fertility have been seen in animal studies (see section 5.3). There are no data on the effect of Clonazepam on fertility in humans.

4.7 Effects on ability to drive and use machines

As a general rule, epileptic patients are not allowed to drive. Even when adequately controlled on clonazepam, increase in dosage or alteration in timings of dosage may modify patients' reactions, depending on individual susceptibility. Clonazepam can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is impaired. This effect is aggravated by consumption of alcohol. Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment.

The decision for allowing the patient to drive rests with their doctor and should be based on the patient's response to treatment and the dosage involved.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you.
- It is an offence to drive while under the influence of this medicine.
- However, you would not be committing an offence (called 'statutory defence')

if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely.

4.8 Undesirable effects

The following have been observed.

Frequencies are defined according to the following convention: 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), not known (cannot be estimated from the available data).

Immune system disorders

Allergic reactions and very rare cases of anaphylaxis have been reported to occur with benzodiazepines. Angioedema may occur in rare cases.

Endocrine disorders

Isolated cases of reversible development of premature secondary sex characteristics in children (incomplete precocious puberty) have been reported.

Psychiatric disorders

Impaired concentration, restlessness, confusional state and disorientation have been observed. Depression may occur in patients treated with clonazepam, but it may be also associated with the underlying disease.

The following paradoxical reactions have been observed: excitability, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, vivid dreams and psychotic disorders and activation of new types of seizures may be precipitated. If these occur, the benefit of continuing the drug should be weighed against the adverse effect. The addition to the regimen of another suitable drug may be necessary or, in some cases, it may be advisable to discontinue clonazepam therapy.

Dependence (see section 4.4)

In rare cases loss of libido may occur.

Nervous system disorders

Somnolence, slowed reaction, muscular hypotonia, dizziness and ataxia. These undesirable effects occur relatively frequently and are usually transient and generally disappear spontaneously in the course of the treatment or on reduction of the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment.

Headache was observed in rare cases. Causing of generalised fits was observed very rarely.

Particularly in long-term or high-dose treatment, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced coordination of movements and gait disorder (ataxia) and nystagmus may occur. Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible.

Although clonazepam has been given uneventfully to patients with porphyria, rarely it may induce convulsions in these patients.

Eye disorders

Particularly in long-term or high-dose treatment, reversible disorders of vision (diplopia) may occur.

Common: nystagmus

Cardiac Disorders

Cardiac failure including cardiac arrest has been reported.

Respiratory, thoracic and mediastinal disorders

Rarely respiratory depression may occur, particularly on intravenous administration of clonazepam. This effect may be aggravated by pre-existing airways obstruction or

brain damage or if other medications which depress respiration have been given. As a rule, this effect can be avoided by careful adjustment of the dose to individual requirements.

In infants and small children, and particularly those with a degree of mental impairment, clonazepam may give rise to salivary or bronchial hypersecretion with drooling. Supervision of the airway may be required.

Gastrointestinal disorders

The following effects have been reported in rare cases: nausea, gastrointestinal and epigastric symptoms

Skin and subcutaneous tissue disorders

The following effects may occur in rare cases: urticaria, pruritus, rash, transient hair loss and pigmentation changes.

Musculoskeletal and connective tissue disorders

Muscle weakness, this undesirable effect occurs relatively frequently and is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It can be partially prevented by increasing the dose slowly at the start of the treatment.

Renal and urinary disorders

In rare cases urinary incontinence may occur.

Reproductive System and breast disorders

In rare cases erectile dysfunction or loss of libido may occur.

General disorders and administration site conditions

Fatigue (tiredness, lassitude), this undesirable effect occurs relatively frequently and is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It can be partially prevented by increasing the dose slowly at the start of treatment.

Withdrawal reactions (see section 4.4)

Investigations

In rare cases decreased platelet count may occur. As with other benzodiazepines, isolated cases of blood dyscrasias and abnormal liver function tests have been reported

Injury, poisoning and procedural complications

There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Paediatric population

For paediatric specific events please refer to the information listed under headings: Endocrine Disorders and Respiratory, Thoracic and Mediastinal System Disorders in section 4.8

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The symptoms of overdosage or intoxication vary greatly from person to person depending on age, bodyweight and individual response. Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of clonazepam is seldom life-threatening if the drug is taken alone, but may lead to coma, areflexia, apnoea, hypotension and cardiorespiratory depression. Coma, if it occurs, usually lasts only a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease.

Benzodiazepines potentiate the effects of other central nervous system depressants, including alcohol.

Management

1. Maintain a clear airway and adequate ventilation if indicated.
2. Supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.
3. Further absorption should be prevented using an appropriate method e.g. treatment within 1 to 2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients.

4. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.
5. Patients who are asymptomatic at 4 hours are unlikely to develop symptoms.
6. Flumazenil (Anexate), a benzodiazepine antagonist is available but should rarely be required. If CNS depression is severe consider the use of flumazenil. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after the effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug. Flumazenil is NOT TO BE USED IN MIXED OVERDOSE OR AS A 'DIAGNOSTIC TEST'.

Warning

The use of flumazenil is not indicated in epileptic patients who have been treated with benzodiazepines. Although flumazenil exerts a slight intrinsic anticonvulsant effect, its abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

If excitation occurs, barbiturates should not be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, benzodiazepine derivate.

ATC code: N03AE01

Mechanism of action

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. Animal data and electroencephalographic investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absences seizures (petit mal), slow spike wave, generalised spike wave, spikes with temporal or other locations as well as irregular spikes and waves.

Generalised EEG abnormalities are more readily suppressed by clonazepam than focal EEG abnormalities such as focal spikes. Clonazepam has beneficial effects in generalised and focal epilepsies.

5.2 Pharmacokinetic properties

Absorption

Clonazepam is quickly and completely absorbed after oral administration. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. Bioavailability is 90% after oral administration.

Routine monitoring of plasma concentrations of clonazepam is of unproven value since this does not appear to correlate well with either therapeutic response or side-effects.

Distribution

The mean volume of distribution of clonazepam is estimated at about 3 L/kg. Clonazepam must be assumed to cross the placental barrier and has been detected in maternal milk.

Metabolism

The biotransformation of clonazepam involves oxidative hydroxylation and reduction of the 7-nitro group by the liver with formation of 7-amino or 7-acetylamino compounds, with trace amounts of 3-hydroxy derivatives of all three compounds, and their glucuronide and sulfate conjugates. The nitro compounds are pharmacologically active, whereas the amino compounds are not.

Elimination

The elimination half-life is between 20 and 60 hours (mean 30 hours).

Within 4 - 10 days 50 - 70% of the total radioactivity of a radiolabelled oral dose of clonazepam is excreted in the urine and 10 - 30% in the faeces, almost exclusively in the form of free or conjugated metabolites. Less than 0.5% appears as unchanged clonazepam in the urine.

Pharmacokinetics in special clinical situations

Based on kinetic criteria no dose adjustment is required in patients with renal failure.

5.3 Preclinical safety data

Carcinogenicity

Conventional studies of carcinogenic potential have not been conducted with clonazepam. However, in an 18-month chronic study in rats no treatment-related histopathological changes were seen up to the highest tested dose of 300 mg/kg/day.

Mutagenicity

Genotoxicity tests using bacterial systems with in vitro or host mediated metabolic activation did not indicate a genotoxic liability for clonazepam.

Impairment of Fertility

Studies assessing fertility and general reproductive performance in rats showed a reduced pregnancy rate and impaired pup survival at doses of 10 and 100 mg/kg/day.

Teratogenicity

No adverse maternal or embryo-foetal effects were observed in either mice or rats following administration of oral clonazepam during organogenesis, at doses of up to 20 or 40 mg/kg/day, respectively.

In several rabbit studies following doses of clonazepam of up to 20 mg/kg/day, a low, non-dose-related incidence of a similar pattern of malformations (cleft palate, open eyelids, fused sternebrae and limb defects) was observed (see section 4.6).

As toxicokinetic evaluations have not been performed with clonazepam, it is not possible to determine the safety margin for the adverse effects observed in the nonclinical studies. The relevance of these findings to the patient population is unclear therefore a potential risk to man cannot be ruled out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate

pregelatinized starch

microcrystalline cellulose

magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC-PVDC/Aluminium blister pack.

Clonazepam Crescent 0.5 mg is available in pack sizes of 30, 60, 50, 100,120 or 150 tablets.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Key House
Sarum Hill, Basingstoke
RG21 8SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0832

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/06/2025

10 DATE OF REVISION OF THE TEXT

19/06/2025