Cabergoline can cause fibrotic reactions and cardiac valvulopathy. Ongoing treatment with cabergoline will require continued monitoring for these adverse events.

AUSTRALIAN PRODUCT INFORMATION – CABASER® (CABERGOLINE) TABLETS

1. NAME OF THE MEDICINE

The active ingredient in CABASER is cabergoline.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CABASER tablets for oral administration contain 1.0 mg or 2.0 mg cabergoline.

Excipient(s) with known effect

Sugars (as lactose).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

1 mg unit dose: white, oval, both sides concave tablets, one side scored and engraved ‘7’ on the left of the break-line and ‘01’ on the right of it.

2 mg unit dose: white, oval, both sides concave tablets, one side scored and engraved ‘7’ on the left of the break-line and ‘02’ on the right of it.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the management of the signs and symptoms of Parkinson’s Disease.

Treatment should be initiated under specialist supervision. The benefit of continued treatment should be regularly reassessed taking into account the risk of fibrotic reactions and valvulopathy (see Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, and Section 4.8 Adverse effects (undesirable effects)).

4.2 Dose and method of administration

Method of administration

CABASER is to be administered by the oral route. Since in clinical studies, CABASER has been mainly administered with food and since the tolerability of dopaminergic agents is improved when administered with food, it is recommended that CABASER be taken with

meals. Food does not appear to have an effect on the absorption of CABASER (see Section 5.2 Pharmacokinetic properties).

There are no data to demonstrate that the 1 mg and 2 mg tablets are bioequivalent when given in equal doses.

CABASER is intended for chronic, long term treatment. (See Section 4.4 Special warnings and precautions for use - Valvulopathy and respiratory disorders linked to fibrotic tissue degeneration.)

Adults and elderly patients

As expected for dopamine agonists, dose response for both efficacy and side effects appears to be mainly linked to individual sensitivity. Optimisation of dose should be obtained through slow initial dose titration from starting doses of 0.5 mg (monotherapy patients) to 1 mg (patients on levodopa). In patients already receiving levodopa, the dosage of this drug may be gradually decreased while the dosage of CABASER is increased until the optimum balance is determined. In view of the long lasting kinetics of the compound, increments of the daily dose of 0.5-1 mg should be done at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.

The recommended therapeutic dosage is 2 to 3 mg/day for patients with signs and symptoms of Parkinson's disease. CABASER should be given as a single daily dose.

The safety and efficacy of doses higher than those recommended have not been established. (See Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects) - Post-marketing experience.)

Use in children

The safety and the efficacy of CABASER have not been investigated in children, as Parkinson's disease does not affect this population.

Use in renal or liver insufficiency

Renal insufficiency has been shown not to modify cabergoline kinetics. Hepatic insufficiency of severe degree (> 10 Child-Pugh score, maximum score 12) has been shown to be associated with an increase of AUC, thus indicating that dose regimens in Parkinsonian patients with severe hepatic insufficiency should be modified accordingly.

4.3 Contraindications

Hypersensitivity to cabergoline, other ergot alkaloids or to any of the excipients.

History of pulmonary, pericardial or retroperitoneal fibrotic disorders.

Anatomical evidence of cardiac valvulopathy of any valve (e.g., echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis).

4.4 Special warnings and precautions for use

CABASER has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with CABASER. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

Postural hypotension can occur following administration of cabergoline, particularly during the first days of administration of Cabaser. Care should be exercised when administering Cabaser concomitantly with drugs known to lower blood pressure.

Use with caution in the following circumstances:

Use in hepatic impairment

Severe hepatic insufficiency (>10 Child-Pugh score, maximum score 12)

Severe hepatic insufficiency has been shown to be associated with an increase of AUC, thus dose regimens in these patients should be modified accordingly. (See Section 5.2 Pharmacokinetic properties)

Valvulopathy and respiratory disorders linked to fibrotic tissue degeneration

Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage of ergot derivatives such as cabergoline. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of cabergoline. Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values.

Serum creatine measurements can also be used to help in the diagnosis of fibrotic disorder.

Valvulopathy has been associated with cumulative doses and has been observed at recommended doses.

Before initiating treatment:

All patients should undergo a cardiovascular evaluation, including an echocardiogram, to assess potential presence of asymptomatic valvular disease. It may be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline (See Section 4.3 Contraindications).

During treatment:

Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis. Therefore during treatment, attention should be paid to the signs and symptoms of:

- Pleuropulmonary disease, such as dyspnoea, shortness of breath, persistent cough, or chest pain.

- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank, and lower limb oedema, as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.

- Cardiac failure, as cases of pericardial fibrosis have often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear.

- Cardiac failure, as cases of valvular fibrosis have often manifested as cardiac failure; valvular fibrosis should be excluded if such symptoms appear.

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is recommended. Following treatment initiation, the first echocardiogram should occur within 3-6 months, thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but should occur at a least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening. (See Section 4.3 Contraindications) The need for other clinical monitoring (e.g., physical examination, careful cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

Severe cardiovascular disease, Raynaud's syndrome, peptic ulcer, gastrointestinal bleeding or a history of serious, particularly psychotic mental disease.

Psychiatric illness

Studies have shown that a past history of psychiatric illness is a predictor of depressive adverse events on CABASER. Screening of such patients who may be more likely to develop depression is therefore recommended.

Compulsive Behaviour

Pathological (compulsive) behaviour such as gambling, increased libido, hypersexuality, shopping, eating, medication use and punding (repetitive purposeless activity) have been reported in patients treated with dopaminergic agents for the treatment of Parkinson’s disease, including cabergoline and levodopa, especially at high doses. This has been generally reversible upon reduction of the dose or treatment discontinuation. Prescribers, patients and caregivers should be alert to the possibility of such behaviour.

Use in the elderly

See Section 4.2 Dose and method of administration - Adults and elderly patients

Paediatric use

The safety and the efficacy of CABASER have not been investigated in children, as Parkinson's disease does not affect this population.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No pharmacokinetic interaction with levodopa or selegiline was observed in the studies carried out in Parkinsonian patients. The concomitant use of other drugs, particularly other anti-Parkinson non-dopamine-agonist agents, was not associated with detectable interactions modifying the efficacy and safety of CABASER.

No information is available about possible interaction between CABASER and other ergot alkaloids: therefore the concomitant use of these medications during long term treatment with CABASER is not recommended.

Since CABASER exerts its therapeutic effect by direct stimulation of dopamine receptors, it should not be concurrently administered with drugs which have dopamine antagonist activity (such as phenothiazines, butyrophenones, thioxanthines, metoclopramide) as these might reduce the therapeutic effect of CABASER.

By analogy with other ergot derivatives, CABASER should not be used in association with macrolide antibiotics (e.g. erythromycin) since the systemic bioavailability and also adverse events could increase.

Mono-oxygenase activity was increased 1.5 to 3 fold in female rats treated with cabergoline 0.1 to 1.5 mg/kg/day orally. Concomitant administration of cabergoline with drugs metabolised by mono-oxygenases may result in altered exposure and activity.

Symptomatic hypotension can occur when administering concomitantly with drugs known to lower blood pressure.

The effects of alcohol on overall tolerability of CABASER are currently unknown.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Fertility of female rats was completely inhibited by cabergoline at oral doses of 3 mg/kg/day and above, while male fertility was not affected at doses up to 320 mg/kg/day. The complete inhibition of fertility in female rats is related to inhibition of prolactin secretion and its effect on nidation.

Use in pregnancy – Pregnancy Category B1

CABASER has been shown to cross the placenta in rats: it is unknown whether this also occurs in humans.

Animal studies in rats and mice have not demonstrated any teratogenic effect or any effect of the compound on global reproductive performance at doses that do not cause maternal toxicity. In clinical studies there have been over 100 pregnancies in women treated with cabergoline for hyperprolactinemic disorders. The compound was generally taken during the first 8 weeks after conception. Among the pregnancies evaluable so far, there were approximately 85% live

births and about 10% spontaneous abortions. Three cases of congenital abnormalities (Down's syndrome, hydrocephalus, malformation of lower limbs) which led to therapeutic abortion and three cases of minor abnormalities in live births were observed. These frequencies are comparable with those quoted for normal populations and for women exposed to other ovulation-inducing drugs. Based on the above data, the use of the product does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy, or congenital abnormalities.

Because clinical experience is still limited and the drug has a long half life, as a precautionary measure it is recommended that women intending to become pregnant discontinue CABASER one month before intended conception in order to prevent possible fetal exposure to the drug. If conception occurs during therapy, treatment is to be discontinued as soon as pregnancy is confirmed to limit fetal exposure to the drug. Women not intending to become pregnant should be advised to use mechanical contraception during treatment. Before CABASER administration, pregnancy should be excluded.

Use in lactation

In rats, cabergoline and/or its metabolites are excreted in milk. Lactation is expected to be inhibited/suppressed by CABASER due to its dopamine-agonist properties. Therefore, while no information on the excretion of cabergoline in maternal milk in humans is available, puerperal women should be advised not to breast-feed in case of failed lactation inhibition/suppression by the product.

4.7 Effects on ability to drive and use machines

During the first days of CABASER administration, patients should be cautioned about re-engaging in activities requiring rapid and precise responses such as driving an automobile or operating machinery. Patients being treated with CABASER and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see Section 4.4 Special warnings and precautions for use).

4.8 Adverse effects (undesirable effects)

About 1070 Parkinsonian patients received CABASER as adjuvant therapy to levodopa in clinical trials. Of these, at least 74% had at least one adverse event, mainly of mild to moderate severity and transient in nature, and requiring discontinuation in a small proportion of cases. Events were related to the nervous system in 51% of the patients, the gastrointestinal system was involved in 33% of the cases, the cardiovascular system was involved in 27% of the cases and the respiratory system was involved in 13% of the cases.

About 200 newly diagnosed patients with Parkinson’s disease have received CABASER as monotherapy in clinical studies, of these 79% reported at least one adverse event, mainly mild and transient in nature. Events were related to the nervous system in 51% of the patients, the gastrointestinal system was involved in 53% of the cases and the cardiovascular system was involved in 30% of the cases.

The majority of events were of mild to moderate severity, transient in nature and requiring discontinuation in a small proportion of cases (15% and 9% with CABASER in the two populations respectively).

In both populations gastric upset was more frequent in female than in male patients, while CNS events were more frequent in the elderly.

In both populations a blood pressure decrease of clinical relevance was observed mainly on standing in a minority of patients. The effect was mainly evident in the first weeks of therapy. Neither modification of heart rate nor consistent changes of ECG tracings were observed during CABASER treatment.

Alterations in standard laboratory tests have been uncommon during long term therapy with CABASER.

Tables 1 and 2 below summarise the frequency of adverse events by most relevant body systems reported during the clinical program with CABASER in the two main patient populations studied. All adverse events occurring with an incidence of 3% or higher in any treatment group are reported in the tables. A dash represents an incidence of less than 3%.

TABLE 1 Advanced Parkinson's Disease Patients

	CABASER (n=1069) %	**Placebo (n=122) %**	**Control (bromocriptine) (n=397) %**
Nervous System			
dyskinesias	16.4	23.0	9.1
dizziness	10.3	10.7	8.3
hallucination	9.0	3.3	8.6
insomnia	7.4	9.8	7.8
headache	5.9	4.9	3.5
somnolence	5.9	-	5.5
confusion	5.8	-	3.3
sleep disorders	5.4	-	7.6
hypokinesia	4.6	13.9	-
Gastrointestinal			
nausea	16.4	10.7	20.7
constipation	4.9	4.1	3.8
vomiting	4.2	-	4.5
Cardiovascular			
orthostatic hypotension	10.5	6.6	12.6
hypotension	3.5	-	5.5
Respiratory			
upper respiratory tract infection	4.3	4.9	-
Body as a whole			
asthenia	3.8	-	4.0

	CABASER (n=1069) %	Placebo (n=122) %	Control (bromocriptine) (n=397) %
peripheral oedema	3.4	-	3.0

TABLE 2 Monotherapy in Newly Diagnosed Parkinson's Disease Patients

	CABASER (n=211) %	Control (levodopa) (n=208) %
Nervous System		
dizziness	27.0	18.7
somnolence	17.5	18.3
depression	13.3	15.4
insomnia	10.9	17.3
anxiety	9.0	11.1
sweating increased	5.2	11.1
headache	7.1	4.3
dyskinesia	3.8	6.3
euphoria	4.7	4.8
hallucination	4.3	4.8
confusion	4.7	3.8
paroniria	4.3	-
Gastrointestinal		
nausea	29.9	25.0
constipation	22.7	15.4
dry mouth	9.5	10.1
gastritis	7.6	6.7
vomiting	4.7	7.2
anorexia	4.3	6.7
diarrhoea	4.3	-
dyspepsia	-	4.3
Cardiovascular		
postural hypotension	10.4	8.2
palpitation	4.3	4.8
hypertension	5.2	-
Respiratory System		
bronchitis	6.6	6.3
upper respiratory tract infection	5.2	-
pneumonia	-	4.3
dyspnoea	3.3	-
Urogenital System		
urinary tract infection	5.7	5.8
Prostatic disorder	3.3	-
Musculo-skeletal system		

	CABASER (n=211) %	Control (levodopa) (n=208) %
osteo-articular injury	4.3	5.8
arthralgia	-	6.7
arthrosis	-	3.8
Body as a whole		
influenza	7.1	8.2
back pain	5.7	5.8
peripheral oedema	8.5	-
legs oedema	5.2	-
death	3.8	-
pain	-	3.4

Post-marketing experience

The following events have been reported in association with CABASER: aggression, alopecia, increased blood creatinine phosphokinase, delusions, oedema, fatigue, fibrosis, abnormal hepatic function, hypersensitivity reaction, hypersexuality, increased libido, abnormal liver function tests, pathological gambling, psychotic disorder, rash, respiratory disorder, respiratory failure somnolence associated with excessive daytime somnolence and sudden sleep onset episodes, and syncope.

There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy and retroperitoneal fibrosis, in patients taking cabergoline (see Section 4.4 Special warnings and precautions for use). The incidence of valvulopathy with cabergoline is not known, however based on recent studies of the prevalence of valvular regurgitation (the most sensitive echocardiographic marker for restrictive valvulopathy), the prevalence of regurgitation (virtually all cases asymptomatic) potentially attributable to cabergoline may be in the range of 20% or greater. There is limited information available on the reversibility of these reactions.

Being an ergot derivative, CABASER may act as a vasoconstrictor. Digital vasospasm and leg cramps have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

There is limited experience of overdosage with CABASER in humans. Symptoms of overdosage would likely be those of over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, hypotension, nasal congestion, syncope, confusion/psychosis or hallucinations.

Treatment of CABASER overdose is symptomatic and supportive. Supportive measures should be directed to maintain blood pressure, if necessary.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

In addition, in case of pronounced central nervous system effects the administration of dopamine antagonist drugs may be advisable.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia)..

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

CABASER is a dopaminergic ergoline derivative with potent and long-lasting dopamine D2 receptor agonist properties. In rats, the compound, acting at D2 dopamine receptors on pituitary lactotrophic cells, decreases prolactin (PRL) secretion at oral doses of 3-25 mg/kg, and *in vitro* at a concentration of 45 pg/mL. In addition, CABASER exerts a central dopaminergic effect via D2 receptor stimulation at doses higher than those effective in lowering serum PRL levels. Improvement of motor deficit in animal models of Parkinson's Disease was present at oral daily doses of 1 - 2.5 mg/kg in rats and at s.c. doses of 0.5 – 1 mg/kg in monkeys.

In healthy volunteers the administration of CABASER at single oral doses of 0.3 - 2.0 mg was associated with a significant decrease in serum PRL levels. The effect is prompt (within 3 hours from administration) and persistent (up to 7 - 28 days). The PRL-lowering effect is dose-related both in terms of degree of effect and duration of action.

The pharmacodynamic actions of CABASER which are not linked to the therapeutic effect relate only to blood pressure decrease. The maximal hypotensive effect of CABASER as a single dose usually occurs during the first 6 hours after drug intake and is dose-dependent both in terms of maximal decrease and frequency.

Clinical trials

CABASER tablets were evaluated for the treatment of signs and symptoms of Parkinson's Disease. Four pivotal trials were conducted, three studies as adjunctive therapy to levodopa and one study as monotherapy treatment of Parkinson's Disease.

Adjunctive Therapy to Levodopa - Treatment of Motor Complications

The first study was a Phase III, double blind, placebo controlled study of the safety and efficacy of CABASER, n=188. CABASER was administered once a day to 123 patients (0.5 mg - 5.0 mg/day) over 6 months. CABASER demonstrated a significantly lowered Unified Rating Scale for Parkinson's Disease (URSPD) of 15%, a significant lowered levodopa sparing effect and lowered values in 'off' scores compared to placebo. A statistically ($p<0.001$) and clinically significantly greater decrease of the levodopa in the CABASER (18%) vs

placebo (3%) groups. Scores for the combined factors II and III of the URSPD were significantly lower (p=0.03) for the CABASER group than for the placebo group: Factor II (Daily living activities, 23% amelioration under CABASER vs 4% under placebo), Factor III (Motor examination, 16% amelioration under CABASER vs 6% under placebo.

The second and third pivotal studies were two Phase III, parallel group, multicentre, double blind studies of the activity and tolerability of CABASER once a day vs bromocriptine t.i.d in Parkinsonian patients suffering from levodopa associated motor complications. The first study (Study 1: CABASER; n=191, 476 days & bromocriptine; n=193, 467 days) involved patients not on treatment with dopamine agonist agents. The second study (Study 2: CABASER; n=181, 447 days & bromocriptine; n=185, 451 days) involved patients on treatment with dopamine agonist agents. Dosages were titrated for both CABASER and bromocriptine, 0.5 mg - 6.0 mg/day and 5 mg – 40 mg/day, respectively. Both studies showed clinical equivalence of the two treatments, defined as a between treatment difference in the response rate (minimal to very much improvement according to Clinical Global Improvement Scale (CGI) lower than 15%. The results at last assessment after the end of stable dose indicate maintenance of improvement in 63% and 60% of the CABASER treated and 58% and 59% of the bromocriptine treated patients in the two studies.

Monotherapy for Parkinson's Disease

The fourth pivotal study was a phase III, double blind, multicentre trial in newly diagnosed Parkinsonian patients. The study evaluated the efficacy of initial treatment with CABASER *vs* levodopa on the development of motor complications upon long term treatment (n=419). The patients were newly diagnosed and never treated with levodopa, dopamine agonists or selegiline. Patients were randomised to either CABASER once a day (n=211, mean duration 1106 days) or levodopa q.i.d (n=208, mean duration 1196 days). Following dose titrations (CABASER 0.25 - 4.0 mg/day and levodopa 100 – 600 mg/day) patients entered a stable dose treatment period of 3 - 5 years duration. During the stable dose period levodopa could be added if clinical improvement could not be maintained with the initial stable dose.

The primary study end point was the time of onset to motor fluctuations confirmed at two subsequent visits at 3 monthly intervals. A total of 47 (22.3%) and 70 (33.6%) CABASER and levodopa patients reached the primary end point.

The analysis of cumulative risk of developing confirmed motor complications showed a statistically significant difference (p=0.0175) in favour of CABASER, the risk of developing motor complications always higher in levodopa patients. The relative risk of motor complications in CABASER treated patients was 54% lower than in levodopa treated patients and more than double in both treatment groups in case of additional levodopa.

A total of 135 (64%) CABASER and 98 (47%) levodopa patients required additional levodopa, cumulative exposure being 304 grams and 203 grams, respectively.

Patients on CABASER required additional levodopa earlier than those already receiving levodopa. Seventy four (55%) CABASER and 39 (40%) levodopa patients required add-on levodopa therapy in the first year of treatment. The difference between the two treatments in the distribution of failures (patients requiring additional levodopa) was statistically significant (p=0.0001).

As to symptomatic efficacy, at all time points the mean values for levodopa were lower than the corresponding values for CABASER for both Factor II and III. No statistically significant

changes were detected with either treatment on other UPDRS factors, Zung Self Depression Scale and Mini Mental State Examination.

5.2 Pharmacokinetic properties

The pharmacokinetic and metabolic profiles of CABASER have been studied in healthy volunteers of both sexes, in female hyperprolactinemic patients and in Parkinsonian patients. After oral administration of the labelled compound, radioactivity was rapidly absorbed from the gastrointestinal tract as the peak of radioactivity in plasma was between 0.5 and 4 hours. Ten days after administration about 20% and 72% of the radioactive dose (^{14}C-cabergoline) was recovered in urine and faeces, respectively. Unchanged drug in urine accounted for 2 - 3% of the dose.

In urine, the main metabolite identified was 6-allyl-8b-carboxy-ergoline, which accounted for 4 - 6% of the dose. Three additional metabolites were identified in urine which accounted overall for less than 3% of the dose. The metabolites have been found to be much less potent than CABASER as D2 dopamine receptor agonists *in vitro.*

The low urinary excretion of unchanged CABASER has also been confirmed in studies with non-radioactive product. The elimination half-life of CABASER, estimated from urinary excretion rates, is long (63 - 68 hours in healthy volunteers, 79 - 115 hours in hyperprolactinemic patients).

The pharmacokinetics of CABASER seem to be linear both in healthy volunteers (doses of 0.5 - 1.5 mg) and Parkinsonian patients (steady state of daily doses up to 7 mg/day).

On the basis of the elimination half-life, steady state conditions should be achieved after 4 weeks, as confirmed by the mean peak plasma levels of CABASER obtained after a single dose (37 +/- 8 pg/mL) and after a 4 week multiple-regimen (101 +/- 43 pg/mL). *In vitro* experiments showed that the drug at concentrations of 0.1 – 10 ng/mL is 41 - 42% bound to plasma proteins.

In limited studies, food did not appear to have an effect on the absorption and disposition of CABASER.

Renal insufficiency has been shown not to modify cabergoline kinetics. Hepatic insufficiency with a Child-Pugh score of less than 10 does not appear to affect the pharmacokinetics of cabergoline. A single study in which 12 patients received 1 mg cabergoline as a single dose, showed that there was no statistical difference in Cmax, Tmax and AUC in patients with mild liver disease group (group A, average Child-Pugh score 5.8) compared to more severe degrees of the disease (group B, average Child-Pugh score 7.5 and group C, average Child-Pugh score 10.5). It was observed however, that the average AUC tended to increase with the severity of the hepatic impairment, particularly in Group C. AUC averaged 957.

5.3 Preclinical safety data

Genotoxicity

Gene mutation and cytogenetic assays *in vitro* and *in vivo* suggest that cabergoline does not possess genotoxic activity.

Carcinogenicity

Two year carcinogenicity studies were conducted in rats and mice at maximum doses of 0.32 and 0.98 mg/kg/day corresponding to exposure (based on AUC) levels 0.86 and 0.72 times that expected in humans. In rats, the oral administration of cabergoline at doses of 0.02 to 0.32 mg/kg/day resulted in an increased incidence of benign Leydig cell tumours in males, and an increased incidence of reproductive tract tumours, such as squamous carcinoma, stromal sarcoma and adenocarcinoma in females. In mice, oral doses of 0.02 to 0.98 mg/kg/day resulted in a low incidence of uterine and cervical leiomyomas and leiomyosarcomas at dose levels of 0.14 mg/kg/day and above. The carcinogenic effects in rodents may involve endocrine mechanisms resulting from disturbances of the hypothalamo-pituitary-gonadal axis secondary to inhibition of prolactin secretion. However, even though there is no known correlation between uterine malignancies occurring in cabergoline treated rodents and human risk, there are no human data to substantiate this conclusion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Leucine

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging'.

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

1 mg unit dose: –Bottles of 30's

2 mg unit dose: –Bottles of 30's.

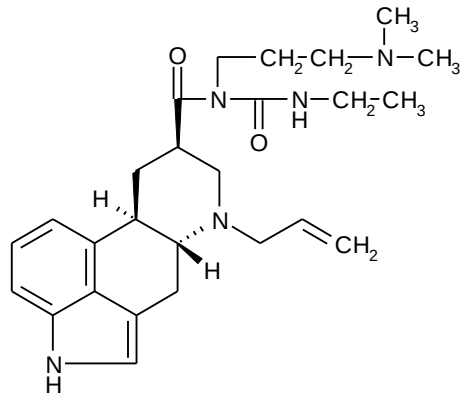
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Cabergoline is (8R)-6-allyl-N-[3-dimethylamino propyl]-N-(ethylcarbamoyl) ergoline-8-carbamoxide.

Chemical structure



PNU-142779 Cabergoline

CAS number

81409-90-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

10 June 2004

10. DATE OF REVISION

20 May 2025

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Summary Table of Changes

Section changed	Summary of new information
2	Correction to expression of excipients with known effect.
8	Update to the medical information web address