Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dalzior 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg cabergoline.

Excipient: lactose 75.8 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, oval- shaped, flat, bevelled tablets containing 0.5 mg cabergoline. Each tablet is scored on one side and has ‘CBG’ on one side and ‘0.5’ on the other side of the breakline.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Inhibition of lactation for medical reasons.

Hyperprolactimaemic disorders

Prolactin secreting pituitary adenomas

Idiopathic hyperprolactinaemia

It is recommended that the medicinal product is initially prescribed by an appropriate specialist or after consulting a specialist.

4.2 Posology and method of administration

Cabergoline is to be administered by the oral route.
In order to reduce the risk of gastrointestinal undesirable effects it is recommended that cabergoline is taken with meals for all therapeutic indications.
The maximum dose of 3 mg/day of cabergoline must not be exceeded.

Adults:

Treatment of hyperprolactinaemic disorders:

The recommended initial dosage is 0.5 mg cabergoline per week given in one or two doses (e.g. on Monday and Thursday) per week. The weekly dose should be increased gradually, preferably by adding 0.5 mg cabergoline per week at monthly intervals until an optimal therapeutic response is achieved.

The therapeutic dosage is usually 1 mg cabergoline per week and ranges from 0.25 mg to 2 mg cabergoline per week. Doses of up to 4.5 mg cabergoline per week have been used in hyperprolactinaemic patients.

The weekly dose may be given as a single administration or divided into two or more doses per week according to patient tolerability. Division of the weekly dose into multiple administrations is advised when doses higher than 1 mg cabergoline per week are to be given since the tolerability of doses greater than 1 mg cabergoline taken as a single weekly dose has been evaluated only in a few patients.
Patients should be evaluated during dose escalation to determine the lowest dosage that produces the therapeutic response.

For inhibition of lactation:

Cabergoline should be administered within the first 24 hours post-partum. The recommended therapeutic dosage is 1 mg cabergoline given as a single dose**.**

Use in patients with hepatic or renal dysfunction.

Use in patients with hepatic insufficiency and renal insufficiency see section 4.4

Inhibition/suppression of physiologic lactation:

A single dose of 0.25 mg cabergoline should not be exceeded in nursing women treated for suppression of established lactation to avoid potential postural hypotension.

Use in children and adolescents:

The safety and efficacy of cabergoline has not been established in subjects less than 16 years of age.

Use in the elderly:

As a consequence of the indications for which cabergoline is presently proposed, the experience in elderly is very limited. Available data do not indicate a special risk.

4.3 Contraindications

Pre-eclampsia, eclampsia
Post-partum hypertension or uncontrolled hypertension.
Hypersensitivity to cabergoline, any ergot alkaloid or to any excipient of the product.
History of pulmonary, pericardial and retroperitoneal fibrotic disorders.
History of psychosis or risk of post-partum psychosis
For long-term treatment: evidence of cardiac valvulopathy as determined by pre-treatment echocardiography (See section 4.4 Special warnings and precautions for use – Fibrosis and cardiac valvulopathy and possibly related clinical phenomena).

4.4 Special warnings and precautions for use

General:

As with other ergot derivatives, cabergoline should be given with caution to subjects with severe cardiovascular disease, hypotension, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding or with a history of serious, particularly psychotic, mental disorders.

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

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

Hepatic insufficiency:
Lower doses should be considered in patients with severe hepatic insufficiency who receive prolonged treatment with cabergoline. Compared to normal volunteers and those with lesser degrees of hepatic insufficiency, an increase in AUC has been seen in patients with severe hepatic insufficiency (Child-Pugh Class C) who received a single 1 mg dose.

Postural hypotension:
Postural hypotension can occur following administration of cabergoline. Care should be exercised when administering cabergoline concomitantly with other drugs known to lower blood pressure.

Fibrosis and cardiac valvulopathy and possibly related clinical phenomena:

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 with agonist activity at the serotonin $5HT_{2B}$ receptor, 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.

Valvulopathy has been associated with cumulative doses, therefore, patients should be treated with the lowest effective dose. At each visit, the risk benefit profile of cabergoline treatment for the patient should be reassessed to determine the suitability of continued treatment with cabergoline.

Before initiating long-treatment:
All patients should undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy.

In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline. (See Section 4.3 Contraindications).

During long-term 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:

- Pleuro-pulmonary disease, such as dyspnoea, shortness of breath, persistent cough, or chest pain.
- Renal insufficiency or ureteral/abdominal vascular obstructions 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; cases of valvular and pericardial fibrosis have often manifested as cardiac failure.

Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of fibrotic disorders, as appropriate, is essential. Following treatment initiation, the first echocardiogram must 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 must occur at 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 including cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.

Additional appropriate investigations such as erythrocyte sedimentation rate, and serum creatinine measurements should be performed if necessary to support a diagnosis of fibrotic disorder.

Hypotension:
Symptomatic hypotension can occur within 6 hours following administration of cabergoline: particular attention should be paid when administering cabergoline concomitantly with other medicical product known to lower blood pressure. Because of its elimination half-life hypotensive effects may persist for a few days after cessation of therapy. Monitoring of treatment with regular checks of blood pressure is recommended in the first 3-4 days after initiation of treatment.

Low blood pressure ($\geq$ 20 mmHg systolic and $\geq$ 10 mmHg diastolic) has been reported in the 3-4 days following a single dose of 1 mg cabergoline in post-partum studies. The undesirable effects generally occur in the first two weeks, and then decline or disappear. 3% of the patients had their treatment discontinued on account of the undesirable effects.

Somnolence/sudden sleep onset*:*
Cabergoline has been associated with somnolence. Dopamine agonists can be associated with sudden sleep onset episodes in patients with Parkinson's disease. A reduction of dosage or termination of treatment may be considered (See section 4.7 Effects on ability to drive and use machines).

Inhibition/suppression of physiologic lactation:
As with other ergot derivatives, cabergoline should not be used in women with pregnancy-induced hypertension, for example, preeclampsia or post-partum hypertension.

A single dose of 0.25 mg of cabergoline should not be exceeded in nursing women treated for suppression of established lactation to avoid potential postural hypotension. (See section 4.2 Posology and method of administration – Inhibition/suppression of physiologic lactation and subsection above – Postural hypotension).

Treatment of hyperprolactinaemic disorders:
Since hyperprolactinaemia accompanied with amenorrhoea/galactorrhea and infertility may be associated with pituitary tumour, a complete evaluation of the pituitary is indicated before treatment with cabergoline is initiated.

Cabergoline restores ovulation and fertility in women with hyperprolactinemic hypogonadism.

Before administration of cabergoline, pregnancy should be excluded. Because clinical experience is still limited and the product has a long half-life, as a precautionary measure it is recommended that once regular ovulatory cycles have been achieved women seeking pregnancy discontinue cabergoline one month before intended conception.

Because pregnancy might occur prior to reinitiation of menses, a pregnancy test is recommended at least every 4 weeks during the amenorrheic period and, once menses are reinitiated, every time a menstrual period is delayed by more than 3 days. Women who wish to avoid pregnancy should be advised to use mechanical contraception during treatment with cabergoline and after discontinuation of cabergoline until recurrence of anovulation. As a precautionary measure, women who become pregnant should be monitored to detect signs of pituitary enlargement since expansion of pre-existing pituitary tumors may occur during gestation.

Monitoring of serum prolactin levels at monthly intervals is advised since, once the effective therapeutic dosage regimen has been reached, serum prolactin normalisation is usually observed within two to four weeks.

After cabergoline withdrawal, recurrence of hyperprolactinaemia is usually observed. However, persistent suppression of prolactin levels has been observed for several months in some patients.

Renal insufficiency:
No overall differences in the pharmacokinetics of cabergoline were observed in moderate to severe renal disease. The pharmacokinetics of cabergoline has not been studied in patients having end-stage renal failure, or in patients on haemodialysis; these patients should be treated with caution.

Psychiatric:
Pathologic gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including cabergoline. This has been generally reversible upon reduction of the dose or treatment discontinuation.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended:

No information is available about interaction between cabergoline and other ergot alkaloids; therefore, the concomitant use of these medications during long-term treatment with cabergoline is not recommended.

Since cabergoline exerts its therapeutic effect by direct stimulation of dopamine receptors, it should not be concurrently administered with drugs that have dopamine-antagonist activity (such as phenothiazines, butyrophenones, thioxanthenes, metoclopramide) since these might reduce the prolactin-lowering effect of cabergoline.

As with other ergot derivatives, cabergoline should not be used with macrolide antibiotics (e.g., erythromycin) due to increased systemic bioavailability of cabergoline.

Precautions:
Interactions with other medicinal products that reduce blood pressure should be taken into consideration.

No pharmacokinetic interactions with L-dopa or selegiline have been observed in studies of patients with Parkinson's disease. Pharmacokinetic interactions with other medicinal products cannot be predicted based on available information about the metabolism of cabergoline.

4.6 Fertility, pregnancy and lactation

Pregnancy
In a twelve year observational study on pregnancy outcomes following cabergoline therapy, information is available on 256 pregnancies. Seventeen of these 256 pregnancies (6.6%) eventuated in major congenital malformations or abortion. Information is available on 23/258 infants who had a total of 27 neonatal abnormalities, both major and minor. Musculoskeletal malformations were the most common neonatal abormality (10), followed by cardio-pulmonary abnormalities (5). There is no information on perinatal disorders or long-term development of infants exposed to intra-uterine cabergoline. Based on recent published literature, the prevalence of major congenital malformations in the general population has been reported to be 6.9% or greater. Rates of congenital abnormality vary between different populations. It is not possible to accurately determine if there is an increased risk as no control group was included.

Before cabergoline administration, pregnancy should be excluded and after treatment pregnancy should be prevented for at least one month. As cabergoline has an elimination half-life of 79-115 hours in hyperprolactinaemic patients, once regular ovulatory cycles have been achieved women seeking pregnancy should discontinue cabergoline one month before intended conception. This will prevent possible foetal exposure to the drug and will not interfere with the possibility of conception since ovulatory cycles persist in some cases for six months after drug withdrawal. If conception occurs during therapy, treatment should be discontinued as soon as pregnancy is confirmed to limit foetal exposure to the drug.

Contraception should be continued for at least 4 weeks after stopping cabergoline.

Cabergoline restores ovulation and fertility in women with hyperprolactinaemic hypogonadism: since pregnancy might occur prior to reinitiation of menses, pregnancy testing is recommended as appropriate during the amenorrhoeic period and, once menses are reinitiated, every time a menstrual period is delayed by more than three days. Women not seeking pregnancy should be advised to use effective non-hormonal contraception during treatment and after cabergoline withdrawal. Because of limited experience on the safety of foetal exposure to cabergoline, it is advisable that women seeking pregnancy conceive at least one month after cabergoline discontinuation.. As a precautionary measure, women who become pregnant should be monitored to detect signs of pituitary enlargement since expansion of pre-existing pituitary tumours may occur during gestation.

Lactation
In rats, cabergoline and/or its metabolites are excreted in milk. No information is available on the excretion in breast milk in humans; however, mothers should be advised not to breast-feed in case of failed lactation inhibition/suppression by cabergoline. Since it prevents lactation, cabergoline should not be administered to mothers with hyperprolactinemic disorders who wish to breast-feed their infants.

4.7 Effects on ability to drive and use machines

Cabergoline reduces blood pressure, which may impair the reactions of certain patients. This should be taken into account in situations requiring intense awareness, such as when driving a car or operating machinery.

Patients treated with cabergoline 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) unless patients have overcome such experiences of somnolence (see section 4.4 Special warnings and precautions for use – Somnolence/sudden sleep onset).

4.8 Undesirable effects

The undesirable effects are usually dose-dependent, and can be reduced by decreasing the dose gradually.

Inhibition of lactation: Approximately 14% of the patients experience undesirable effects. The most common are low blood pressure (12%), dizziness (6%) and headaches (5%). Long-term treatment increases the frequency of undesirable effects to approximately 70%.

The following undesirable effects have been observed and reported during treatment with cabergoline with the following frequencies: 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).

General		
MedDRA System Organ Class	**Frequency**	**Adverse Events**
Vascular disorders	**Common**	Cabergoline generally exerts a hypotensive effect in patients on long-term treatment; postural hypotension
	Uncommon	Digital vasospasm, fainting
Musculoskeletal and connective tissue disorders	**Uncommon**	Leg cramps
Investigations	**Uncommon**	A decrease in haemoglobin values has been observed in amenhorrheic women during the first few months after menses
Hyperprolactinemic Disorders		
MedDRA System Organ Class	**Frequency**	**Adverse Events**
Psychiatric disorders	**Common**	Depression, sleep disturbances
	Not Known	Aggression, hypersexuality, pathological gambling
Nervous system disorders	**Very Common**	Dizziness/vertigo, headache
	Not Known	Sudden sleep onset, syncope
	Uncommon	Paresthesia
Vascular disorders	**Common**	Hot flushes
Gastrointestinal disorders	**Very Common**	Abdominal pain/dyspepsia/gastritis, nausea
	Common	Constipation, vomiting
Reproductive system and breast disorders	**Common**	Breast pain
General disorders and administration site conditions	**Very Common**	Asthenia/fatigue
Inhibition/Supression of Lactation		
MedDRA System Organ Class	**Frequency**	**Adverse Events**
Nervous system disorders	**Common**	Dizziness/vertigo, headache, somnolence
	Uncommon	Transient hemianopsia, Syncope
Cardiac disorders	**Uncommon**	Palpitations
	Very common	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)
Respiratory, thoracic and mediastinal disorders	**Uncommon**	Epistaxis
	Uncommon	Pleural effusion, pulmonary fibrosis
Gastrointestinal disorders	**Common**	Abdominal pain, nausea
	Uncommon	Vomiting
	Rare	Epigastric pain
Investigations	**Common**	Asymptomatic decreases in blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic)
Vascular disorders	**Uncommon**	Hot flushes
General disorders and administration site conditions	**Uncommon**	Asthenia

Vision	**Not Known**	Abnormal Vision

Others

Cardiac disorders
Common: chest pain
Eye Disorders
Uncommon: Hemianopsia.
Skin and subcutaneous tissue disorders
Common: facial redness
Musculoskeletal and connective tissue disorders
Rare: Cramp in fingers and calves.
The following events have been reported in association with cabergoline:
Hallucinations

4.9 Overdose

Symptoms of overdose would likely be those of over-stimulation of dopamine receptors, e.g., nausea, vomiting, gastric complaints, postural hypotension, reduced blood pressure, confusion/psychosis or hallucinations.

Supportive measures should be taken to remove unabsorbed drug and maintain blood pressure, if necessary. In addition, the administration of dopamine antagonist drugs may be advisable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prolactin inhibitor

ATC code: G02CB03

Cabergoline is a synthetic ergot alkaloid and an ergoline derivate with long-acting dopamine agonist and prolactin-inhibiting properties. A central dopaminergic effect via D2-receptor stimulation is achieved through higher doses than doses that reduce the levels of serum prolactin.

The prolactin-reducing effect is dose-dependent, starting within 3 hours and remaining for 2-3 weeks. The long-acting effect means that a single dose is generally sufficient to stop the initiation of milk secretion. In treatment of hyperprolactinaemia, the serum prolactin levels are generally normalised within two to four weeks of the optimal dose being attained. Prolactin can still be significantly reduced several months after withdrawal of the treatment.

With regard to the endocrine effects of cabergoline not related to the antiprolactinaemic effect, available data from humans confirm the experimental findings in animals indicating that the test compound is endowed with a very selective action with no effect on basal secretion of other pituitary hormones or cortisol.

The pharmacodynamic actions of cabergoline not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of cabergoline as single dose usually occurs during the first 6 hours after active substance intake and is dose-dependent both in terms of maximal decrease and frequency.

5.2 Pharmacokinetic properties

Absorption

After oral administration cabergoline is rapidly absorbed from the gastrointestinal tract as the peak plasma concentration is received within 0.5 to 4 hours.

Food does not appear to affect absorption and disposition of cabergoline.

Distribution

"In-vitro" experiments showed that cabergoline at concentrations of 0.1 – 10 ng/ml is 41-42% bound to plasma proteins.

Biotransformation

In urine, the main metabolite identified is 6-allyl-8ß-carboxy-ergoline, which accounts for 4-6% of the dose. Three additional metabolites are identified in urine, which account overall for less than 3% of the dose. The metabolites have been found to be much less potent than cabergoline in inhibiting prolactin secretion "in-vitro".

Elimination

The elimination half-life of cabergoline, is long; (63-68 hours in healthy volunteers and 79-115 hours in hyperprolactinaemic patients).

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 cabergoline obtained after a single dose (37 ± 8 pg/ml) and after a 4 week multiple-regimen (101 ± 43 pg/ml) for 0.5mg cabergoline dose.

Ten days after administration about 18% and 72% of the dose is recovered in urine and faeces, respectively. Unchanged cabergoline in urine accounts for 2-3% of the dose.

Linearity/Non-linearity

The pharmacokinetic profile is linear up to 7 mg per day.

5.3 Preclinical safety data

Almost all the findings noted throughout the series of preclinical safety studies are a consequence of the central dopaminergic effects or the long-lasting inhibition of PRL in species (rodents) with a specific hormonal physiology different to man.

Preclinical safety studies of cabergoline indicate a large safety margin for this compound in rodents and in monkeys, as well as a lack of teratogenic, mutagenic or carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous lactose
L-Leucine
Magnesium stearate (E572)

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 moisture.

The drying capsule or bag with silica gel must not be removed from the bottle.

6.5 Nature and contents of container

Brown glass bottles (type III) that contain a desiccation capsule or bag with silica gel. The brown glass bottle has an induction-sealed childproof aluminium membrane and a childproof HDPE or Polypropylene top. External box.

Packaging sizes: 2, 8, 14, 15, 16, 20, 28, 30, 32, 40, 48, 50, 60, 90, 96, 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Norton Waterford
trading as IVAX Pharmaceuticals Ireland
Unit 301
IDA Industrial Park
Cork Road
Waterford
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 436/45/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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