1.3.1.1 APPROVED PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOXURRA 0,5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of DOXURRA contains 0,5 mg cabergoline.

Contains sugar: Lactose anhydrous 75,9 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

DOXURRA is a white to off-white, capsule shaped, flat, bevelled edge, uncoated tablet engraved with “43” on one side and score line on other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DOXURRA is indicated for:

- Inhibition of lactation before the commencement of breastfeeding as well as inhibition of established lactation for medical reasons. Not recommended for the routine suppression of lactation or for the relief of symptoms of postpartum pain and

engorgement, which can be adequately treated with simple analgesics and breast support.

- Treatment of hyperprolactinemic disorders.

4.2. Posology and method of administration

Posology

Adults

For inhibition of lactation

DOXURRA should be administered during the first day post-partum. The recommended therapeutic dosage is 1 mg (two 0,5 mg tablets) given as a single dose.

For suppression of established lactation

The recommended therapeutic dosage regimen is 0,25 mg (one-half 0,5 mg tablet) every 12 hours for two days (1 mg total dose). DOXURRA should not be administered as a single dose greater than 0,25 mg in this indication since this reduces tolerability.

For treatment of hyperprolactinemic disorders

The recommended initial dosage is 0,5 mg given in one or two doses per week. The weekly dose should be increased gradually, preferably by adding 0,5 mg per week at monthly intervals until an optimal therapeutic response is achieved.

The therapeutic dosage is usually 1 mg per week and ranges from 0,25 mg to 2 mg per week. Doses up to 4,5 mg per week have been used.

The dosage should preferably be adjusted according to prolactin blood levels.

Division of the weekly dose into multiple administrations is advised when doses higher than 1 mg per week are to be given.

Patients should be evaluated during dose escalation to determine the lowest dosage that produces the therapeutic response. Monitoring of serum prolactin levels at monthly intervals is advised.

Once the effective therapeutic dosage regimen has been reached, serum prolactin normalisation is usually observed within two to four weeks.

Special populations

Elderly population

DOXURRA has not been formally studied in elderly patients with hyperprolactinemic disorders.

Hepatic impairment

DOXURRA is contraindicated in patients with hepatic insufficiency.

Paediatric population

Safety and efficacy have not been established in patients younger than 16 years.

Method of administration

For oral administration, preferably taken with meals.

4.3. Contraindications

DOXURRA is contraindicated in:

- Patients with hypersensitivity to cabergoline, any ergot alkaloid or to any excipients in DOXURRA (see section 6.1).
- Pregnancy and breastfeeding (see section 4.6).
- Women with pre-eclampsia or post-partum hypertension.

- History of pulmonary, pericardial and retroperitoneal fibrotic disorders.
- Patients with hepatic insufficiency and with toxaemia of pregnancy.
- Co-administration with anti-psychotic medicines or administered to women with a history of puerperal psychosis.
- Patients with evidence of cardiac valvulopathy as determined by pre-treatment echocardiography when initiating long-term therapy (see section 4.4).

4.4. Special warnings and precautions for use

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, as in DOXURRA. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of cabergoline, as in DOXURRA.
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 (see section 4.3). Therefore, DOXURRA should be used with caution in patients with a history of, or current signs and/or clinical symptoms of, respiratory or cardiac disorders linked to fibrotic tissue.

Following diagnosis of pleural effusion/pulmonary fibrosis or valvulopathy, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms in small minority of affected patients.

General

The safety and efficacy of DOXURRA have not been established in patients with renal and hepatic disease.

DOXURRA should be given with caution to patients with cardiovascular disease, Raynaud's syndrome, renal insufficiency, peptic ulcer, gastrointestinal bleeding or history of psychotic, mental disorders.

Particular care should be taken when patients are taking concomitant psychoactive medicines.

Symptomatic / Postural hypotension

Symptomatic hypotension can occur with DOXURRA administration for any indication, monitoring of blood pressure is advised, and care should be exercised when administering DOXURRA concomitantly with other medicines known to lower blood pressure.

Pregnancy

Before DOXURRA administration, pregnancy should be excluded and after treatment pregnancy should be prevented for at least one month (see sections 4.3 and section 4.6).

Hepatic insufficiency

Since available data indicated that biliary excretion represents the main route of elimination of DOXURRA, it is advisable not to administer the drug to subjects with severe liver insufficiency (see section 4.3). 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.

Somnolence/Sudden sleep onset

Cabergoline, as in DOXURRA has been associated with somnolence. Dopamine agonists can be associated with sudden sleep onset episodes in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported less frequently (see section 4.8). Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with DOXURRA. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction in dosage or termination of therapy may be considered (see section 4.7).

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating, and compulsive eating can occur in patients treated with dopamine agonists including DOXURRA. Dose reduction/tapered discontinuation should be considered if such symptoms develop (see section 4.8).

Inhibition/suppression of physiological lactation

As with other ergot derivatives, DOXURRA should not be used in women with pregnancy-induced hypertension, for example, preeclampsia or post-partum hypertension, (see section 4.3)

In post-partum studies with cabergoline, as in DOXURRA, blood pressure decreases were mostly asymptomatic and were frequently observed on a single occasion 2 to 4 days after treatment. Since decreases in blood pressure are frequently noted during the puerperium, independently of medicine therapy, it is likely that many of the observed decreases in blood pressure after cabergoline, as in DOXURRA, administration were not medicine-induced. However, periodic monitoring of blood pressure, particularly during the first few days after DOXURRA administration, is advised.

A single dose of 0,25 mg of DOXURRA should not be exceeded in nursing women treated for suppression of established lactation to avoid potential postural hypotension (see section 4.2).

A clinical study exploring the efficacy and tolerability of 0,5 mg of cabergoline, as in DOXURRA, given as a single dose for suppression of lactation has shown that the risk of side effects is approximately doubled in this indication if the medicine is administered as a single dose of 0,5 mg.

Treatment of hyperprolactinaemic disorders

Since hyperprolactinemia with amenorrhea/galactorrhea and infertility may be associated with pituitary tumours, a complete evaluation of the pituitary is indicated before treatment with DOXURRA is initiated.

Before initiating long-term treatment

All patients must 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 DOXURRA treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with DOXURRA (see section 4.3).

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 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: 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 to 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.
DOXURRA should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening (see section 4.3).

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 a fibrotic disorder.

Risk of medicine withdrawal syndrome

Dopamine receptor agonists can induce medicine withdrawal syndrome (see section 4.8). Cases of medicine withdrawal syndrome have been reported.

Excipients

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

Paediatric population

The safety and efficacy of DOXURRA has not been established in patients younger than 16 years.

4.5. Interaction with other medicines and other forms of interaction

Other ergot alkaloids

The concomitant use of other medicines during early puerperium, particularly of ergot alkaloids, was not associated with detectable interactions modifying the efficacy and safety of cabergoline, as in DOXURRA (see section 4.3).

Although there is no conclusive evidence of an interaction between DOXURRA and other ergot alkaloids, the concomitant use of these medicines during therapy with DOXURRA is not recommended.

Dopamine antagonists

Since DOXURRA exerts its therapeutic effect by direct stimulation of dopamine receptors, it should not be concurrently administered with medicines which have dopamine antagonist activity (such as phenothiazines, butyrophenones, thioxanthenes, metoclopramide), since these might reduce the prolactin-lowering effect of DOXURRA (see section 4.4).

Macrolide antibiotics

DOXURRA should not be used with macrolide antibiotics (e.g. erythromycin) due to the increased systemic bioavailability of cabergoline.

Medicines known to lower blood pressure

Symptomatic hypotension can occur with DOXURRA administration for any indication. Care should be exercised when administering cabergoline concomitantly with other medicines known to lower blood pressure (see section 4.4).

4.6. Fertility, pregnancy and lactation

The use of DOXURRA in confirmed or suspected pregnancy and breastfeeding is contraindicated (see section 4.3).

Women of childbearing potential

Due to the long half-life of cabergoline, as in DOXURRA, and limited data on in utero exposure, women planning to become pregnant should discontinue DOXURRA one month

before intended conception. If conception occurs during therapy, treatment should be discontinued as soon as pregnancy is confirmed to limit foetal exposure to DOXURRA.

Women who do not wish to become pregnant should use a mechanical contraceptive during the treatment and after discontinuation until the ovulatory cycles cease.

Pregnancy

Before DOXURRA is administered, pregnancy must be excluded and after treatment pregnancy must be prevented for at least a month.

Pregnancy could occur in women treated for hyperprolactinemic hypogonadism before restoration of the menstrual cycle; it is advisable to carry out a pregnancy test at least every four weeks during the period of amenorrhea and afterwards every time the menstrual period is delayed by more than three days.

When pregnancy is confirmed during the treatment, the use of DOXURRA should be suspended, and as a precautionary measure, pituitary size should be monitored since expansion of pre-existent tumours could occur during pregnancy.

Cabergoline, as in DOXURRA, restores ovulation and fertility in women with hyperprolactinaemic hypogonadism.

Because pregnancy might occur prior to re-initiation of menses, a pregnancy test is recommended at least every four weeks during the amenorrhoeic period and, once menses are reinitiated, every time a menstrual period is delayed by more than three days. Women who wish to avoid pregnancy should be advised to use mechanical contraception during treatment with DOXURRA and after discontinuation of DOXURRA until recurrence of anovulation (see section 4.6).

Before administration of DOXURRA, pregnancy should be excluded (see section 4.3).

Because clinical experience is still limited and DOXURRA has a long half-life, as a

precautionary measure it is recommended that once regular ovulatory cycles have been achieved women seeking pregnancy, discontinue DOXURRA one month before intended conception. Should pregnancy occur during treatment, DOXURRA is to be discontinued. 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 (see section 4.6).

Regular gynaecological assessment, including cervical and endometrial cytology, is recommended for patients taking DOXURRA for extensive periods.

Breastfeeding

Animal studies have shown that cabergoline, as in DOXURRA, and/or its metabolites are excreted in milk. No information is available on the excretion in breast milk in humans; however, women should not breastfeed in case of failed lactation inhibition/suppression by DOXURRA. Since it prevents lactation, DOXURRA should not be administered to mothers with hyperprolactinemic disorders who wish to breastfeed their infants.

Fertility

No data available.

4.7. Effects on ability to drive and use machines

DOXURRA can have major influence on the ability to drive and operate machinery.

Patients should be careful when performing actions which require fast and accurate reaction during treatment initiation.

During the first days of DOXURRA administration, patients should be cautioned about reengaging in activities requiring rapid and precise responses such as driving an automobile or operating machinery.

Since adverse reactions such as somnolence, dizziness and visual impairment have been reported in patients receiving DOXURRA, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that DOXURRA does not adversely affect their ability to do so (see sections 4.4 and 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

DOXURRA generally exerts a hypotensive effect in patients. Symptoms mainly appear during the first two weeks of therapy and disappear despite continued therapy.

Being an ergot derivative, DOXURRA may also act in some patients as a vasoconstrictor.

Valvulopathy and fibrosis have been reported in association with cabergoline, as in DOXURRA.

Adverse events are generally dose-related. In patients known to be intolerant to dopaminergic medicines, the likelihood of adverse events may be lessened by starting therapy with DOXURRA at reduced doses, e.g. 0,25 mg once a week, with subsequent gradual increase until the therapeutic dosage is reached. If persistent or severe adverse events occur, temporary reduction of dosage followed by a more gradual increase, e.g. increments of 0,25 mg/week every two weeks, may increase tolerability.

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Immune system disorders		Hypersensitivity reaction	
Psychiatric disorders	Depression		
		Increased libido	Aggression, delusions, hypersexuality, pathological gambling, psychotic disorder, hallucinations
Nervous system disorders	Dizziness/vertigo, headache,	Transient hemianopsia,	
	somnolence	syncope,	
		paraesthesia	
			Sudden sleep onset, tremor
Eye disorders			Visual impairment
Cardiac disorders		Palpitations	
	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)		Angina pectoris
Vascular disorders	Hot flushes		
	Hypotensive effects (long-term treatment), postural hypotension	Digital vasospasm, fainting	
Respiratory, thoracic and mediastinal disorders		Epistaxis,	
		dyspnoea, pleural effusion, fibrosis, (including pulmonary fibrosis), pleural fibrosis	Respiratory disorder, respiratory failure, pleuritis, chest pain
Gastrointestinal disorders	Abdominal pain, nausea	Epigastric pain,	
	dyspepsia, gastritis, constipation, vomiting		
Hepato-biliary disorders			Hepatic function abnormal

Skin and subcutaneous tissue disorders		Rash, alopecia	
Musculoskeletal and connective tissue disorders		Leg cramps	
Reproductive system and breast disorders	Breast pain		
General disorders and administrative site conditions	Asthenia, fatigue		
		Oedema, peripheral oedema	
			Medicine withdrawal symptoms such as apathy, anxiety, depression, fatigue, sweating and pain
Investigations	Asymptomatic decreases in blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic)		
		Decrease in haemoglobin values have been observed in amenorrhoeic women during the first few months after menses.	Increased blood creatinine phosphokinase, liver function tests abnormal

c) *Description of selected adverse reactions*

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including DOXURRA (see section 4.4).

.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

There is no experience in humans of overdosage with cabergoline, as in DOXURRA used in the proposed indications.

Overdosage is likely to lead to symptoms due to over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, postural hypotension, hallucination or thought/perception disturbances.

Treatment

General supportive measures should be undertaken to remove any unabsorbed medicine and maintain blood pressure if necessary. In addition, the administration of dopamine antagonist medicines may be advisable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A 21.12 Hormone inhibitors

Pharmacotherapeutic group: Prolactin inhibitors,

ATC code: G02CB03

Mechanism of action

Cabergoline is a dopaminergic ergoline derivative with a potent and long-lasting prolactin-lowering activity. It acts by direct stimulation of the D_2-dopamine receptors on pituitary lactotrophs, thus selectively inhibiting prolactin secretion.

In addition, cabergoline exerts a central dopaminergic effect via D_2-receptor stimulation at oral doses higher than those effective in lowering serum prolactin levels.

The long-lasting prolactin-lowering effect of cabergoline is probably due to its long persistence in the target organ as suggested by the slow elimination of total radioactivity from the pituitary after a single oral dose in rats (t½ of approximately 60 hours).

The pharmacodynamic effects of cabergoline have been studied in healthy volunteers, puerperal women and hyperprolactinaemic patients. After a single oral administration of cabergoline (0,3 mg to 1,5 mg) a significant decrease in serum prolactin levels was observed in each of the populations studied. The effect is prompt (within 3 hours from administration) and persistent (up to 7 to 28 days in healthy volunteers and hyperprolactinemic patients and up to 14 to 21 days in puerperal women). The prolactin lowering effect is dose-related, both in terms of degree of effect and duration of action.

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 has a 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 a single dose usually occurs during the first 6 hours after intake and is dose-dependent both in terms of maximal decrease and frequency.

5.2. Pharmacokinetic properties

Absorption

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

Distribution

In vitro experiments showed that the medicine at concentrations of 0,1 ng/mL to 10 ng/mL is 41 % to 42 % bound to plasma proteins.

Biotransformation

In urine, the main metabolite identified was 6-allyl-8β-carboxy-ergoline, which accounted for 4 % to 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 cabergoline in inhibiting prolactin secretion *in vitro*. Cabergoline biotransformation was also studied in plasma of healthy male volunteers treated with [^{14}C]-cabergoline: a rapid and extensive biotransformation of cabergoline was shown.

Elimination

The low urinary excretion of unchanged cabergoline has been confirmed also in studies with non-radioactive product. The elimination half-life of cabergoline, estimated from urinary excretion rates, is long (63 to 68 hours in healthy volunteers and 79 to 115 hours in hyperprolactinemic 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 pg/mL ± 8 pg/mL) and after a 4 week multiple regimen (101 pg/mL ± 43 pg/mL).

Biliary excretion is the main route of elimination.

Ten days after administration about 18 % and 72 % of the radioactive dose was recovered in urine and faeces, respectively. Unchanged medicine in urine accounted for 2 % to 3 % of the dose.

In rats cabergoline and/or its metabolites are excreted in milk; no information on its excretion in maternal milk in humans is available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose anhydrous, L-Leucine.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

6.5. Nature and contents of container

DOXURRA is packed into an amber glass bottle and sealed with a white, aluminium, roll on pilfer proof (ROPP) cap containing silica gel. The amber glass bottle is packed into an outer carton. Pack sizes of 2 or 4 tablets.

DOXURRA is packed into an HDPE bottle, with a silica gel canister and sealed with a PP screw cap with an induction wad. The HDPE bottle is packed into an outer carton. Pack sizes of 2 or 4 tablets.

Not all packs or pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Hotline: 0800 122 912

8. REGISTRATION NUMBER

50/21.12/0103

9. DATE OF FIRST AUTHORISATION

15 April 2025

10. DATE OF REVISION OF TEXT

15 April 2025

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.