**PROPOSED PROFESSIONAL INFORMATION**

## SCHEDULING STATUS

S5

## 1. NAME OF THE MEDICINE

DETRYP 10 mg film coated tablets

DETRYP 25 mg film coated tablets

DETRYP 50 mg film coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DETRYP 10 mg: each film coated tablets contains 10 mg amitriptyline hydrochloride.

Contains sugar (lactose monohydrate 18,822 mg per tablet).

DETRYP 25 mg: each film coated tablets contains 25 mg amitriptyline hydrochloride.

Contains sugar (lactose monohydrate 27,833 mg per tablet).

DETRYP 50 mg: each film coated tablets contains 50 mg amitriptyline hydrochloride.

Contains sugar (lactose monohydrate 55,666 mg per tablet).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film coated tablet.

DETRYP 10 mg: Pink coloured, round biconvex, film-coated tablets imprinted with ‘L4’in black ink on one side and plain on other side.

DETRYP 25 mg: Light green coloured, round biconvex, film-coated tablets imprinted with ‘L80’ in black ink on one side and plain on other side.

DETRYP 50 mg: Brick-red coloured, round biconvex, film-coated tablets imprinted with ‘L81’ in black ink on one side and plain on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

DETRYP is indicated for:

- Treatment of endogenous depression.
- Adjunctive therapy for nocturnal enuresis in children over 6 years of age where organic pathology has been excluded.

### 4.2 Posology and method of administration

**Posology**

**Depression:**

*Initial:*

One tablet (25 mg) three times per day increasing gradually to 150 mg daily if necessary. Additional doses should be taken in the late afternoon or evening. Therapy may also be initiated with a single dose of 50 to 100 mg at night increased by 25 or 50 mg as necessary to a total of 150 mg daily. The antidepressant activity may be evident within three or four days or may take up to 30 days to develop adequately.

*Maintenance:*

50 to 100 mg daily.

Treatment should be continued for at least three months before being gradually withdrawn. Hospitalised patients may be given doses of up to 200 mg daily and, occasionally, up to 300 mg daily.

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***Nocturnal enuresis:***

Children 6 to 10 years: 10 to 20 mg at bedtime

Children 11 to 16 years: 25 to 50 mg at bedtime

Do not exceed the recommended dose.

*Duration of treatment*

Treatment should not be continued for longer than 3 months.

When stopping treatment, amitriptyline should be withdrawn gradually.

**Method of administration**

DETRYP is for oral use.

The tablets should be swallowed with water.

**Missed dose:**

Doctors should advise patients who forget to take DETRYP to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

**4.3 Contraindications**

- hypersensitivity to amitriptyline hydrochloride, tricyclic antidepressants or to any of the ingredients of DETRYP
- the acute-phase after myocardial infarction and in patients with heart block
- history of myocardial infarction, dysrhythmias, congestive heart failure, coronary artery insufficiency
- for the treatment of depression in children
- patients receiving monoamine oxidase inhibitors or for at least 14 days after their

discontinuation

- concurrent use with linezolid (see section 4.5)
- concurrent use with antihypertensive medicines (see section 4.5)
- pregnancy and lactation (see section 4.6)
- severe liver disease
- mania (see section 4.4).

**4.4 Special warnings and precautions for use**

**DETRYP should at all times be kept out of the reach of children, as even small doses may be fatal to them.**

*Anticholinergic effects*

Peripheral anticholinergic side effects, notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation. When anticholinergic effects are severe, DETRYP should be discontinued or reduced.

*Sedative effects*

At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery for at least several days. In these situations, impaired decision making could lead to accidents as drowsiness or excessive sedation may be caused in certain patients (see section 4.7). On the other hand, disorientation and agitation, insomnia and restlessness can also occur with normal doses. The risks of central nervous system depression are greater when administered together with other central nervous system depressants, e.g. alcohol, barbiturates.

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*Elderly patients*

Elderly patients are more prone to all these effects, and therapy should be initiated at lower than standard doses in the elderly.

Elderly patients are particularly susceptible to orthostatic hypotension.

In elderly male patients suffering from prostatism, urinary retention may be precipitated.

*Manic depressive psychosis*

Caution should be exercised with patients suffering from a depressive phase of manic-depressive psychosis, as occasionally hypomania or mania can be precipitated in such patients. Withdraw DETRYP if the depression turns into a manic phase.

*Cardiac disease*

In patients suffering from cardiac disease, special caution should be observed because of the occasional problems of tachycardia, dysrhythmias orthostatic hypotension and other unwanted effects on blood pressure, aggravation of conduction disturbances and electrocardiographic abnormalities. Regular cardiological and electrocardiographic examination is advised.

QT interval prolongation and dysrrhythmia can occur. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging medicines. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the prodysrhythmic risk.

*Endocrine effects*

Endocrine effects include changes in libido, interference with sexual function, gynaecomastia and breast enlargement, and galactorrhoea. Changes in blood sugar concentrations may also occur and, less frequently, inappropriate secretion of antidiuretic hormone.

*Cautious use in certain conditions*

Great care is necessary if DETRYP is administered to patients with hyperthyroidism or to those receiving thyroid medication, since cardiac dysrhythmias may develop (see section 4.5).

DETRYP should be used with caution in patients with convulsive disorders, urinary retention, prostatic hypertrophy, paranoid symptomatology and advanced hepatic or cardiovascular disease, pylorus stenosis, constipation or paralytic ileus as some of these conditions may be aggravated by DETRYP.

In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked. Narrow-angle glaucoma may be aggravated.

Epilepsy may be aggravated. DETRYP should be used with caution in patients with a history of epilepsy, and in those with impaired liver function or phaeochromocytoma.

*Hyponatraemia*

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants such as DETRYP and should be considered in all patients who develop drowsiness, confusion or convulsions while taking DETRYP (an antidepressant).

**NOTE:** Elderly patients are more prone to all these effects, and therapy should be initiated at lower than standard doses in the elderly.

*Diabetic patients*

Blood sugar concentrations may be altered in diabetic patients. As described for other psychotropics, DETRYP may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition, the depressive illness itself may affect patients' glucose balance.

*Porphyria*

The use of DETRYP in patients suffering from acute forms of porphyria, especially variegate porphyria and to a lesser extent acute intermittent porphyria and hereditary coproporphyria, is contentious, and thus DETRYP should be used with caution in these patients.

*Skin conditions*

DETRYP should be withdrawn if allergic skin reactions appear.

***Co-administration of certain medicines***

*Direct-acting sympathomimetics*

DETRYP should not usually be given to patients receiving other central nervous system depressants, e.g. barbiturates, and to patients receiving monoamine oxidase inhibitors – only after a suitable interval has elapsed (the medicines may be given together if the dosages are carefully controlled, preferably in hospital). The pressor effects of the direct-acting sympathomimetic medicines, adrenaline (ephinephrine) and noradrenaline (norephinephrine),

are enhanced. The simultaneous administration of anticholinergic medicines may be dangerous. The hypotensive effect of certain antihypertensive medicines may be reduced.

*Electroconvulsive therapy*

Unless essential, it is inadvisable to combine DETRYP and electroconvulsive therapy (ECT).

*Suicide/suicidal thoughts*

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide- related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo- controlled clinical trials of antidepressant medicines in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany DETRYP therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Hyperpyrexia has been reported with tricyclic antidepressants, such as DETRYP, when administered with anticholinergic or with neuroleptic medicines, especially in hot weather.

DETRYP should be used with caution in patients receiving SSRIs (see sections 4.2 and 4.5).

After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability.

*Nocturnal enuresis*

An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.

Amitriptyline for enuresis should not be combined with an anticholinergic drug.

Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis.

*Lactose warning*

DETRYP contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DETRYP. DETRYP may have an effect on the glycaemic control of patients with diabetes mellitus (see 4.4 – *diabetic patients*).

**Paediatric population**

Not recommended for children or adolescents below the age of 18 years Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see section 4.2).

## 4.5 Interaction with other medicines and other forms of interaction

- ***Analgesics:*** increased anticholinergic side-effects with nefopam; increased analgesia with morphine. Increased risk of CNS toxicity when tricyclics given with tramadol.
- ***Muscle relaxants***: Tricyclics enhance muscle relaxant effect of baclofen.
- ***Nitrates***: reduced effect of sublingual nitrates (owing to dry mouth).

**Contraindicated combinations:**

MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) – can potentiate the effects of tricyclic antidepressants such as DETRYP and hyperpyretic crises, severe convulsions, and fatalities have occurred. Also, an increased risk of developing “serotonin syndrome” (see section 4.3).

Treatment with DETRYP should only commence after at least 14 days after the discontinuation of a monoamine oxidase inhibitor as severe hypertensive reactions and have been reported with concomitant use. Conversely, several days should elapse between withdrawing a tricyclic antidepressant such as DETRYP and starting a monoamine oxidase inhibitor.

Concomitant use of DETRYP and linezolid may result in CNS excitation and hypertension (see section 4.3).

**Combinations that are not recommended:**

*Sympathomimetic medicines*: Amitriptyline may potentiate the cardiovascular effects of adrenaline (epinephrine), ephedrine, isoprenaline, noradrenaline (norepinephrine),

phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

*Adrenergic neurone blockers*: Tricyclic antidepressants including DETRYP may counteract the antihypertensive effects of centrally acting antihypertensives such as reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with DETRYP. There is an increased risk of hypertension on clonidine withdrawal.

*Anticholinergic medicines*: Tricyclic antidepressants, including DETRYP may potentiate the effects of these medicines on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, urinary retention or acute glaucoma (especially in elderly patients).

*Medicines which prolong the QT-interval* including antidysrhythmics such as quinidine, amiodarone, disopyramine, procainamide and propafenone, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, and sotalol may increase the likelihood of ventricular dysrhythmias when taken with tricyclic antidepressants including DETRYP.

*Methadone:* Use caution when using DETRYP and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

*Duiretics:* Caution is also advised for co-administration of DETRYP and diuretics inducing hypokalaemia (e.g. furosemide) as there is an increased risk of postural hypotension.

*Thioridazine*: Co-administration of DETRYP and thioridazine (CYP2D6 substrate) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects.

*Tramadol*: Concomitant use of tramadol (a CYP2D6 substrate) and tricyclic antidepressants (TCAs), such as DETRYP increases the risk for seizures and serotonin syndrome. Additionally,

this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

*Antifungals* such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and *torsade de pointes* have occurred.

*Alpha$_2$-adrenoceptor stimulants:* Concomitant use of apraclonidine and brimonidine with DETRYP should be avoided.

*Disulfiram:* Concomitant use of disulfiram may inhibit the metabolism of amitriptyline. Delirium has been reported in patients taking DETRYP with disulfiram.

*Dopaminergics:* Concomitant use of DETRYP and entacapone should be avoided. CNS toxicity has also been reported with selegiline.

**Combinations requiring precautions for use:**

*CNS depressants*: DETRYP may enhance the sedative effects of alcohol, barbiturates and other central nervous system (CNS) depressants and anticonvulsants (i.e. carbamazepine).

*Antihypertensives:* The effects of bethanidine, debrisoquine, guanethidine and possibly of clonidine are reduced by tricyclic antidepressants

*Norepinephrine reuptake inhibitors (NRI):* Concomitant use of DETRYP and reboxetine should be used with caution.

*Anaesthetics*: Concomitant therapy with DETRYP and anesthetics may increase the risk of dysrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being treated with DETRYP.

Patients taking thyroid preparations may show an accelerated response to DETRYP. The use of DETRYP with thyroid hormones may precipitate cardiac dysrhythmias.

**Potential of other medicines to affect amitriptyline:**

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*Tricyclic antidepressants (TCA)* including DETRYP are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population. Other isozymes involved in the metabolism of amitriptyline (as in DETRYP) are CYP3A4, CYP1A2 and CYP2C9.

*CYP2D6 inhibitors*: The CYP2D6 isozyme can be inhibited by a variety of medicines, e.g. neuroleptics, serotonin reuptake inhibitors (SSRIs), beta blockers, and anti-dysrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine and quinidine. These medicines may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Consider to monitor TCA plasma levels, whenever a TCA is to be co-administered with another medicine known to be an inhibitor of CYP2D6. Dose adjustment of DETRYP may be necessary (see section 4.2).

*Other Cytochrome P450 inhibitors*: Cimetidine, methylphenidate and calcium-channel blockers (e.g. diltiazem and verapamil) may increase plasma levels of tricyclic antidepressants and accompanying toxicity. *Antifungals* such as fluconazole (CYP2C9 inhibitor) and terbinafine (CYP2D6 inhibitor) have been observed to increase serum levels of amitriptyline and nortriptyline. Serious adverse effects have been reported due to increased amitriptyline plasma concentration.

*The CYP3A4 and CYP1A2 isozymes* metabolise amitriptyline (as in DETRYP) to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase amitriptyline plasma concentrations and this combination should be avoided. Clinically relevant interactions may be expected with concomitant use of DETRYP and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir. Ritonavir may increase the serum levels of amitriptyline. Therefore, careful monitoring of therapeutic and adverse effects is recommended when these medicines are administered concomitantly.

*Tricyclic antidepressants and neuroleptics* mutually inhibit the metabolism of each other; this may lead to a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these medicines.

*Cytochrome P450 inducers*: Oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine and St. John's Wort (*Hypericum perforatum*) may increase the metabolism of tricyclic antidepressants such as DETRYP and result in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

In the presence of ethanol, amitriptyline free plasma concentrations and nortriptyline concentrations were increased.

DETRYP plasma concentration can be increased by sodium valproate and valpromide. Clinical monitoring is therefore recommended.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

DETRYP should not be taken during pregnancy.

Safety in pregnancy and lactation has not been established – only limited data is available.

Animal studies have shown reproductive toxicity (see section 5.3).

**Breastfeeding**

DETRYP should not be taken during breastfeeding.

Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0,6 % - 1 % of the maternal dose). A risk to the breastfed child cannot be excluded.

**Fertility**

No data on the effects of amitriptyline (as in DETRYP) on human fertility are available.

### 4.7 Effects on ability to drive and use machines

At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery. In these situations, impaired decision making could lead to accidents.

Since adverse reactions such as drowsiness, dizziness and blurred vision have been reported in patients receiving DETRYP, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that DETRYP does not adversely affect their ability to do so (see section 4.8).

### 4.8 Undesirable effects

#### a) Summary of the safety profile

Amitriptyline may induce side effects similar to other tricyclic antidepressants. Some of the side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressive state improves.

#### b) Tabulated summary of adverse reactions

| **System Organ Class** | **Frequency** | **Side effects** |
|---|---|---|
| Blood and lymphatic system disorders | Less frequent | Bone marrow depression including agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, purpura |
| Immune system disorders | Less frequent | Allergic skin rash, urticaria, photosensitisation, oedema of face and tongue, angioedema |
| Endocrine disorders | Less frequent | Syndrome of inappropriate ADH secretion (SIADH), hyperglycaemia, hypoglycaemia, hyponatraemia |

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| | | |
|---|---|---|
| Metabolism and nutrition disorders | Less frequent | Decreased appetite, increased appetite, weight gain, weight loss, anorexia |
| | Frequency unknown | Elevation or lowering of blood sugar levels |
| Psychiatric disorders | Frequent | Aggression, confusional states, agitation |
| | Less frequent | Hypomania or mania, anxiety, insomnia, nightmares, delirium (in elderly patients), hallucinations, suicidal ideation or behaviour, disorientation, excitement, restlessness, disturbed concentration, behavioural changes |
| | Frequency unknown | Paranoia |
| Nervous system disorders | Frequent | Somnolence, tremors, dizziness, headache, drowsiness or excessive sedation, speech disorders (dysarthria), disturbance in attention, dysgeusia, paraesthesia, ataxia |
| | Less frequent | Convulsions, akathisia, polyneuropathy, peripheral neuropathy, numbness, incoordination, tremors, coma, epileptiform seizures, altered EEG, extrapyramidal disorder including abnormal involuntary movements and tardive dyskinesia, dysarthria |
| Eye disorders | Frequent | Accommodation disorder, mydriasis, blurred vision |
| | Less frequent | Acute glaucoma |
| | Frequency unknown | Dry eye |
| Ear and labyrinth disorders | Less frequent | Tinnitus |

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| | | |
|---|---|---|
| Cardiac disorders | Frequent | Palpitations, tachycardia, atrioventricular block, bundle branch block |
| | Less frequent | Myocardial infarction, heart block, non-specific ECG changes and changes in AV-conduction, dysrhythmias, cardiomyopathies, *torsades de pointes* |
| | Frequency unknown | Hypersensitivity myocarditis, sudden death, worsening of cardiac failure |
| Vascular disorders | Frequent | Orthostatic hypotension, hypotension |
| | Less frequent | Hypertension, syncope, stroke |
| Respiratory, thoracic and mediastinal disorders | Frequent | Congested nose |
| | Less frequent | Allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome) |
| Gastrointestinal disorders | Frequent | Dry mouth, constipation, nausea, sour or metallic taste, gastric irritation |
| | Less frequent | Diarrhoea, vomiting, tongue oedema, salivary gland enlargement, paralytic ileus, epigastric distress, dysgeusia, stomatitis, black tongue |
| Hepato-biliary disorders | Less frequent | Jaundice, hepatic impairment (e.g. cholestatic liver disease), hepatitis |

| | | |
|---|---|---|
| Skin and subcutaneous tissue disorders | Frequent<br><br>Less frequent<br><br><br>Frequency unknown | Hyperhidrosis<br><br>Rash, urticaria, face oedema, alopecia, photosensitivity reaction<br><br>Pruritis |
| Musculoskeletal, connective tissue and bone disorders | Frequency unknown | Increased risk of bone fractures (class effect) |
| Renal and urinary disorders | Frequent<br><br>Less frequent | Micturition disorders, urinary retention<br><br>Urinary tract dilation |
| Reproductive system and breast disorders | Frequent<br><br><br>Less frequent | Erectile dysfunction, impotence, changes in libido, sexual dysfunction<br><br>Galactorrhoea, gynaecomastia, breast enlargement, testicular swelling |
| General disorders and administrative site conditions | Frequent<br><br>Less frequent | Fatigue, feeling thirsty, hyperthermia<br><br>Pyrexia, weakness |
| Investigations | Frequent<br><br><br><br>Less frequent | Abnormal electrocardiogram, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia<br><br>Liver function test abnormal, blood alkaline phosphatase increased, transaminases increased |

**c) Description of selected adverse reactions**

***Withdrawal symptoms***:

The symptoms associated with withdrawal of tricyclic antidepressants such as DETRYP, particularly after prolonged administration, include gastrointestinal disturbances such as nausea; generalised somatic symptoms such as malaise, chills, headache, itching and

increased perspiration; irritability, restlessness, anxiety and agitation; sleep disturbances (insomnia and vivid dreams); parkinsonism or akasthisia; hypomania or mania (reported rarely, occurring within 2-7 days of stopping chronic therapy with tricyclic antidepressants); cardiac dysrhythmias. These symptoms are not indicative of addiction. Withdrawal symptoms seem to be more common and more severe in children.

Adverse reactions such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants in the last trimester of pregnancy.

**d) Other special populations**

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs (see section 4.8). The mechanism leading to this increased risk is unknown.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

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## 4.9 OVERDOSE

**Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic**. There is considerably individual variability in response to overdose. Children are especially susceptible to cardiotoxicity, seizures and hyponatraemia. During awakening possibly again confusion, agitation and hallucinations and ataxia.

**Signs and symptoms**:

Overdosage and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects and cardiotoxicity. The following symptoms and signs are characteristic of acute overdosage: drowsiness, restlessness, ataxia, stupor, coma, pyrexia, palpitations, tachycardia, cardiac arrhythmias and hypotension. Epileptiform seizures may occur. Marked antimuscarinic effects may occur, including dryness of the mouth, dilated pupils, tachycardia, urinary retention and intestinal stasis. Severe symptoms include unconsciousness, convulsions and myoclonus, hyperreflexia, hypotension and respiratory and cardiac depression, with life-threatening cardiac arrhythmias that may recur some days after apparent recovery.

Mixed poisoning with other central nervous system depressants is not uncommon.

***Cardiac symptoms***: Dysrhythmias (ventricular tachydysrhythmias, *torsade de pointes*, ventricular fibrillation). The ECG characteristically show prolonged PR interval, widening of the QRS-complex, QT prolongation, T-wave flattening or inversion, ST segment depression, and varying degrees of heart block progressing to cardiac standstill. Widening of the QRS-complex usually correlates well with the severity of the toxicity following acute

overdoses. Heart failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia, hyponatraemia.

**Management of overdose**: Treatment is symptomatic and supportive.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant)

ATC code: N 06 AA 09

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)

**Mechanism of action**

Amitriptyline is a tricyclic antidepressant. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline (norepinephrine) and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiate their action in the brain.

This is associated with the antidepressant activity.

### 5.2 Pharmacokinetic properties

**Absorption:**

Oral administration of the tablets results in a maximum serum levels in about 4 hours ($t_{max}$ =3,89±1,87 hours; range 1,93-7,98 hours). After per oral administration of 50 mg the mean $C_{max}$ =30,95±9,61 ng/ml;

range 10,85-45,70 ng/ml (111,57±34,64 nmol/l; range 39,06 -164,52 nmol/l). The mean absolute oral bioavailability is 53 % (Fabs = 0,527±0,123; range 0,219-0,756).

After oral administration amitriptyline is absorbed slowly but completely. Due to the often-delayed gastrointestinal tract passage maximum plasma concentrations are reached after 1 to 5 (-8) hours.

**Distribution:**

The apparent volume of distribution ($V_d$)β estimated after intravenous administration is 1221 L ± 280 L; range 769-1702 L (16±3 L/kg).

The plasma protein binding is about 95 %.

Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

In nursing mothers' amitriptyline and nortriptyline are excreted in small amounts with the breast milk. The ratio milk concentration/plasma concentration in women is around 1:1. The estimated daily infant exposure (amitriptyline + nortriptyline) averages 2 % of the corresponding maternal weight related doses of amitriptyline (in mg/kg) (see section 4.6).

**Biotransformation:**

*In vitro* the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are CYP1A2 and CYP2C9. The metabolism is subject to genetic polymorphism. The main active metabolite is the secondary amine, nortriptyline.

Nortriptyline is a more potent inhibitor of noradrenaline (norephinephrine) than of serotonin uptake, while amitriptyline inhibits the uptake of noradrenaline (norephinephrine) and serotonin equally well. Other metabolites such as cis- and trans-10-hydroxyamitriptyline

and cis- and trans-10-hydroxynortriptyline have the same profile as nortriptyline but is considerably weaker.

Demethylnortriptyline and amitriptyline N oxide are only present in plasma in minute amounts; the latter is almost inactive. All the metabolites are less anticholinergic than amitriptyline and nortriptyline. In plasma the amount of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

**Elimination:**

The elimination half-life (t½ β) amitriptyline after peroral administration is about 25 hours (24,65±6,31 hours; range 16,49-40,36 hours). The mean systemic clearance (Cls) is 39,24±10,18 L/h, range 24,5353,73 L/h.

The excretion proceeds mainly with urine. The renal elimination of unchanged amitriptyline is insignificant (about 2 %).

Steady state plasma levels of amitriptyline + nortriptyline are reached within a week for most patients, and in steady state the plasma level comprises approximately equal parts of amitriptyline and nortriptyline

around the clock following treatment with conventional tablets 3 times a day.

**Pharmacokinetics in special patient groups**

***Elderly patients***

Longer half-lives and decreased oral ($Cl_0$) clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

***Reduced hepatic function***

Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients (see section 4.2).

***Reduced renal function***

Renal failure has no influence on the kinetics.

***Polymorphism***

The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19) (see section 4.2).

***Pharmacokinetic/pharmacodynamic relationship***

Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

The therapeutic plasma concentration in major depression is around 80 – 200 ng/ml (≈ 280 – 700 nmol/l) (for amitriptyline + nortriptyline). Levels above 300-400 ng/ml are associated with increased risk of disturbance in cardiac conduction in terms of prolonged QRS-complex or AV block.

## 5.3 Preclinical safety data

The genotoxic potential of amitriptyline has been investigated in various *in vitro* and *in vivo* studies. Although these investigations revealed partially contradictory results, particularly a potential to induce chromosome aberrations cannot be excluded. Long-term carcinogenicity studies have not been performed.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

**PROPOSED PROFESSIONAL INFORMATION**

***Tablet core***:

Colloidal silicon dioxide

Hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

***Film coating (Combined excipients of each Opadry variant):***

D and C red, yellow

FD and C blue, red, yellow

Iron oxide yellow

Hypromellose

Macrogol

Titanium dioxide

***Printing ink Opacode black***

Ammonium hydroxide

Black iron oxide

Propylene glycol

Shellac (20% Esterified in Ethanol)

**6.2 Incompatibilities**

Not applicable

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Store at or below 25 °C.

Dispense/store in a tight, light-resistant container.

### 6.5 Nature and contents of container

Round, white HDPE Bottles and PP Caps containing 30, 100 or 1000 tablets.

The 30 and 100 pack size are contained in printed outer cartons.

### 6.6 Special precautions for disposal

No special requirements.

## 7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

## 8. REGISTRATION NUMBER(S)

DETRYP 10 mg: A55/1.2/0232.229

**PROPOSED PROFESSIONAL INFORMATION**

DETRYP 25 mg: A55/1.2/0233.230

DETRYP 50 mg: A55/1.2/0234.231

## 9. DATE OF FIRST AUTHORISATION

06 December 2022

## 10. DATE OF REVISION OF THE TEXT