PROPOSED CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

DIRENTO SR 150 mg (150 mg sustained-release tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each **DIRENTO SR 150 mg** sustained-release tablet contains 150 mg of bupropion hydrochloride.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

DIRENTO SR 150 mg: A light green film-coated, round, biconvex, bevelled edge tablet debossed with **M** over **U12** on one side of the tablet and blank on the other side.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

DIRENTO SR 150 mg is indicated for the treatment of depression as defined by DSM IV Criteria.

After a satisfactory response, continuation with **DIRENTO SR 150 mg** therapy is effective in preventing relapse and preventing recurrence of further depressive episodes.

4.2 Posology and method of administration:

Posology:

Therapy should be initiated by medical practitioners experienced in the treatment of depression.

Use in Adults:

Initial treatment:

The initial dose is 150 mg taken as a single daily dose.

The full antidepressant effect of **DIRENTO SR 150 mg** may not be evident until after several weeks of treatment.

Patients who are not responding adequately to a dose of 150 mg/day may benefit from dose increases up to a maximum of 300 mg/day.

The maximum single dose should not exceed 150 mg.

Doses of **DIRENTO SR 150 mg** greater than 150 mg/day should be taken as a twice daily dose with an interval of at least 8 hours between successive doses. Insomnia is a very common adverse event.

Insomnia may be reduced by avoiding dosing at bedtime (provided there is at least 8 hours between doses) or, if clinically indicated, dose reduction.

Maintenance therapy:

DIRENTO SR 150 mg (300 mg/day) may be effective during long-term treatment (up to 1 year).

Special populations:

Hepatic Impairment:

DIRENTO SR 150 mg should be used with caution in patients with liver impairment. Because of increased variability in the pharmacokinetics in patients with mild hepatic cirrhosis, a reduced frequency of dosing should be considered (see **Undesirable effects** and **Special warnings and precautions for use**). **DIRENTO SR 150 mg** is contra-indicated in patients with severe hepatic cirrhosis.

Method of administration:

DIRENTO SR 150 mg sustained-release tablets should be swallowed whole and not crushed or chewed.

4.3 Contraindications:

- Hypersensitivity to bupropion or any ingredients in the tablets (see section 6.1).
- Patients with a seizure disorder.
- Do not administer to patients already being treated with any other preparation that contains bupropion, as the incidence of seizures is dose dependent.
- Patients undergoing abrupt discontinuation of alcohol or sedatives.
- Patients with a current or previous diagnosis of bulimia or anorexia nervosa, as a higher incidence of seizures was observed in these patients when an immediate release form of bupropion was administered.

- Concomitant administration of monoamine oxidase inhibitors (MAOIs). At least 14 days is necessary between the discontinuation of MAOIs and start of treatment with
  DIRENTO SR 150 mg.
- Severe liver disease.

4.4. Special warnings and precautions for use:

Do not exceed the recommended dose of **DIRENTO SR 150 mg**, as bupropion is associated with a dose-related risk of seizure.

At up to the maximum recommended daily dose (150 mg of **DIRENTO SR 150 mg** twice daily), the incidence of seizures is approximately 0,1 %; the risk appears to be strongly associated with the presence of pre-disposing risk factors. Therefore **DIRENTO SR 150 mg** should not be administered to patients with one or more conditions pre-disposed to a lowered seizure threshold, such as:

- history of head trauma
- central nervous system (CNS) tumour
- history of seizures
- concomitant administration of other medications known to lower the seizure threshold
- excessive use of alcohol or sedatives (see **Contraindications**)
- diabetes treated with hypoglycaemics or insulin
- use of stimulants or anorectic products.

Caution is also necessary in clinical conditions associated with an increased risk of seizures.

DIRENTO SR 150 mg should be discontinued and not recommended in patients who experience a seizure while on treatment.

Clinical worsening and suicide risk associated with psychiatric disorders:

Patients with major depressive disorders - adults and children:

May experience worsening of their depression and/or the emergence of suicidal ideation and behaviours, whether or not they are taking antidepressant medications.

This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treatment with **DIRENTO SR 150 mg** should,

nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at the time of dose changes, either increases or decreases.

Because of the possibility of co morbidity between major depressive disorders and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive order as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania and mania. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing **DIRENTO SR 150 mg**, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, **DIRENTO SR 150 mg** should be tapered.

DIRENTO SR 150 mg should be discontinued promptly if patients experience hypersensitivity reactions during treatment (see **Undesirable effects**).

Medical practitioners should be aware that symptoms may persist beyond the discontinuation of **DIRENTO SR 150 mg** and clinical management should be provided accordingly.

Bupropion is extensively metabolised in the liver to active metabolites, which are further metabolised. No statistically significant differences in the pharmacokinetics of bupropion were observed in patients with mild hepatic cirrhosis compared with healthy volunteers, but bupropion plasma levels showed a higher variability between individual patients.

DIRENTO SR 150 mg should be used with caution in patients with mild hepatic impairment and reduced frequency of dosing should be considered.

All patients with hepatic impairment should be closely monitored for possible side-effects (e.g., insomnia, dry mouth, seizures) that could indicate high bupropion or metabolite levels.

Bupropion is extensively metabolised in the liver to active metabolites which are further metabolised and excreted by the kidneys.

Therefore, treatment of patients with renal impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible side-effects (e.g., insomnia, dry mouth, seizures) that could indicate high bupropion or metabolite levels, toxic effects of elevated blood and tissue levels of bupropion and metabolites.

Clinical experience with bupropion has not identified any differences in tolerability between older and other adult patients. Greater sensitivity of some elderly individuals cannot be ruled out. Elderly patients are more likely to have decreased renal function; hence a reduced frequency of dosing may be required (see **Pharmacokinetics**).

Clinical experience with **DIRENTO SR 150 mg** in patients receiving electroconvulsive therapy (ECT) is limited. Caution should be exercised in patients receiving ECT therapy concomitantly with **DIRENTO SR 150 mg.**

There is limited clinical experience of the use of **DIRENTO SR 150 mg** to treat depression in patients with cardiovascular disease. Care should be exercised it is used in these patients.

Neuropsychiatric symptoms have been reported (see **Undesirable effects**).

Psychotic and manic symptomatology has been reported (see **Undesirable effects**).

DIRENTO SR 150 mg may precipitate a manic episode in patients with bipolar disorder. Aggression, rage and violent behaviour may occur.

Brugada syndrome

Bupropion may unmask Brugada syndrome, a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. Caution is advised in patients with Brugada syndrome or a family history of cardiac arrest or sudden death.

Paediatric population:

The safety and efficacy of **DIRENTO SR 150 mg SR** tablets in patients under 18 years of age have not been established.

4.5. Interaction with other medicines and other forms of interaction:

In vitro findings indicate that bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 IIB6 (CYP2B6) (see **Pharmacokinetics**).

Care should therefore be exercised when **DIRENTO SR 150 mg** is co-administered with medicines known to affect the CYP2B6 isoenzyme (e.g. orphenadrine, cyclophosphamide, ifosfamide).

Although bupropion is not metabolised by the CYP2D6 isoenzyme, *in vitro* human P450 studies have shown that bupropion and hydroxybupropion are inhibitors of the CYP2D6 pathway. In a human pharmacokinetic study, administration of bupropion increased plasma levels of desipramine. This effect was present for at least 7 days after the last dose of bupropion.

Concomitant use of **DIRENTO SR 150 mg** with other medicines metabolised by the CYP2D6 isoenzyme (such as certain beta-blockers, anti-dysrhythmics, selective serotonin re-uptake inhibitors, tricyclic antidepressants and antipsychotics) has not been formally studied.

Therefore, concomitant therapy with substances predominantly metabolised by this isoenzyme should be initiated at the lower end of the dose range of the concomitant medication. If **DIRENTO SR 150 mg** is added to the treatment regimen of a patient already receiving a medication metabolised by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index (see **Pharmacokinetics**). Since bupropion is extensively metabolised, the co-administration of medicines known to induce metabolism (e.g. carbamazepine, phenobarbitone, phenytoin) or inhibit metabolism may affect its clinical activity.

Although citalopram (a SSRI) is not primarily metabolised by CYP2D6, in one study, bupropion, as in **DIRENTO SR 150 mg,** increased the C_{max} and AUC of citalopram by 30 % and 40 %, respectively.

There have been reports of neuropsychiatric events or reduced alcohol tolerance. The intake of alcohol during **DIRENTO SR 150 mg** treatment should be minimised or avoided.

Clinical data suggest a higher incidence of adverse events in patients receiving concurrent administration of bupropion and levodopa. Administration of **DIRENTO SR 150 mg** to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

Concomitant use of **DIRENTO SR 150 mg** and a Nicotine Transdermal System (NTS) may result in elevations of blood pressure.

4.6. Fertility, pregnancy and lactation:

Safety in pregnancy and lactation has not been established.

As bupropion and its metabolites are excreted in human breast milk, mothers should be advised not to breastfeed while taking **DIRENTO SR 150 mg.**

4.7. Effects on ability to drive and use machines:

DIRENTO SR 150 mg tablets may affect the ability to perform tasks that require judgement or motor and cognitive skills. Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain **DIRENTO SR 150 mg** tablets do not adversely affect their performance.

4.8 Undesirable effects:

Immune system disorders*:	
Frequent:	Hypersensitivity reactions such as urticaria.
Less frequent:	More severe hypersensitivity reactions including angioedema, dyspnoea/ bronchospasm and anaphylactic shock. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness. *see also **Skin and subcutaneous tissue disorders**
Metabolism and nutritional disorders:	
Frequent:	Anorexia, weight loss.
Less frequent:	Blood glucose disturbances.

Psychiatric disorders:	
Frequent:	Insomnia, agitation, anxiety.
Less frequent:	Confusion, depression, aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams, depersonalisation, delusions, paranoid ideation, suicidal ideation and suicidal behaviour, psychosis.
Nervous system disorders:	
Frequent:	Headache, tremor, dizziness, taste disorders.
Less frequent:	Concentration disturbance, seizures (see **Special warnings and precautions for use**), dystonia, ataxia, Parkinsonism, incoordination, memory impairment, paraesthesia, syncope.
Eye disorders:	
Frequent:	Visual disturbance.
Ear and labyrinth disorders:	
Frequent:	Tinnitus.
Cardiac disorders:	
Less frequent:	Tachycardia, palpitations.
Vascular disorders:	
Frequent:	Increased blood pressure (sometimes severe), flushing.
Less frequent:	Vasodilation, postural hypotension.
Gastrointestinal disorders:	
Frequent:	Dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation.
Hepatobiliary disorders:	
Less frequent:	Elevated liver enzymes, jaundice, hepatitis.
Skin and subcutaneous tissue disorders*:	
Frequent:	Rash, pruritus, sweating.
Less frequent:	Erythema multiforme and Stevens-Johnson syndrome, exacerbation of psoriasis. *See also **Immune system disorders**

Musculoskeletal and connective tissue disorders:	
Less frequent:	Twitching.
Renal and urinary disorders:	
Less frequent:	Urinary frequency and/or retention.
General disorders and administration site conditions:	
Frequent:	Fever, asthenia, chest pain.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

In addition to those events reported under **Undesirable effects and Warnings and special precautions**, overdose may include drowsiness, loss of consciousness, and/or electrocardiogram (ECG) changes such as conduction disturbances (including QRS prolongation), dysrhythmias and tachycardia. QTc prolongation has also been reported but was generally seen in conjunction with QRS prolongation and increased heart rate.

Treatment:

In the event of overdose, hospitalisation is advised. ECG and vital signs should be monitored.

Ensure an adequate airway, oxygenation and ventilation. Gastric lavage may be indicated if performed soon after ingestion. The use of activated charcoal is also recommended. No specific antidote for **DIRENTO SR 150 mg** is known.

5. PHARMACOLOGICAL PROPERTIES:

5.1. Pharmacodynamic properties:

A 1.2 Psycho-analeptics (antidepressants)

Bupropion is an inhibitor of the neuronal re-uptake of catecholamines norepinephrine (noradrenaline) and dopamine with minimal effect on the re-uptake of indolamines(serotonin). It does not inhibit monoamine oxidase. The mechanism of action of bupropion is unknown.

5.2 Pharmacokinetic properties:

Absorption:

Peak plasma concentrations of bupropion are achieved within 3 hours after oral administration of bupropion tablets to healthy volunteers.

After chronic administration of 150 to 300 mg per day, linear kinetics are exhibited by bupropion and its metabolites.

Absorption of bupropion is not significantly affected when taken with food.

Distribution:

Bupropion is widely distributed with an apparent volume of distribution of approximately 2000 ℓ. Bupropion and hydroxybupropion are moderately bound to plasma proteins (84 % and 77 %, respectively). The extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Biotransformation:

Metabolism of bupropion in humans is extensive. Three pharmacologically active metabolites have been identified in plasma: hydroxybupropion and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion and are of clinical importance. Their plasma concentrations are as high or higher than those of bupropion. Peak plasma concentrations of hydroxybupropion and threohydrobupropion after approximately 6 hours following administration of a single dose of **DIRENTO SR 150 mg**.

Erythrohydrobupropion cannot be measured in the plasma after a single dose of

DIRENTO SR 150 mg.

The active metabolites are further metabolised to inactive metabolites and excreted in the urine. In vitro studies indicate that bupropion is metabolised to its major active metabolite hydroxybupropion primarily by CYP2B6, while cytochrome P450s are not involved in the formation of threohydrobupropion

(see **Interaction with other medicines and other forms of interaction**). Bupropion and hydroxybupropion are both relatively weak competitive inhibitors of the CYP2D6 isoenzyme with Ki values of 21 and 13,3 µM, respectively.

In human volunteers known to be extensive metabolisers of the CYP2D6 isoenzyme, co-administration of bupropion and desipramine has resulted in 2- and 5-fold increases in the C_{max} and AUC, respectively, of desipramine. This effect was present for at least 7 days after the last dose of bupropion. Since bupropion is not metabolised by the CYP2D6 pathway, desipramine is not anticipated to affect the pharmacokinetics of bupropion. Caution is advised when **DIRENTO SR 150 mg** is administered with substrates for the CYP2D6 pathway (see **Interaction with other medicines and other forms of interaction**). In humans, there is no evidence of enzyme induction of bupropion or hydroxybupropion in volunteers or patients receiving recommended doses of bupropion for 10 to 45 days.

Elimination:

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87 % and 10 % of the radioactive dose were recovered in the urine and faeces, respectively. The fraction of the dose bupropion excreted unchanged was only 0,5 %, a finding consistent with the extensive metabolism of bupropion. Less than 10 % of this ^{14}C dose was accounted for in the urine as active metabolites. The mean apparent clearance following oral administration of bupropion is approximately 200 ℓ/hr and the mean elimination half-life of bupropion is approximately 20 hours.
The elimination half-life of hydroxybupropion is approximately 20 hours and its area under the plasma concentration versus time curve (AUC) at steady state is approximately 17 times that of bupropion. The elimination half-lives for threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively) and steady-state AUC values are 8 and 1,6 times higher than that of bupropion, respectively. Steady state for bupropion and its metabolites is reached within 8 days.

Patients with renal impairment:

The pharmacokinetics of bupropion in renal impairment has not been studied. The reduced renal function may affect the elimination of the major metabolites of bupropion (see **Undesirable effects and Special warnings and precautions for use**).

Patients with hepatic impairment:

Pharmacokinetics of bupropion and its active metabolites were not statistically significantly different in patients with mild cirrhosis when compared to healthy volunteers. More variability was observed between individual patients. For patients with severe hepatic cirrhosis, a single dose of bupropion produced a C_{max} and AUC that were substantially

increased (mean difference approximately 70 % and 3-fold, respectively) and more variable when compared to the values in healthy volunteers; the mean half- life was also longer (by approximately 40 %). For the metabolites, the mean C_{max} was lower (by approximately 30 to 70 %), the mean AUC tended to be higher (by approximately 30 to 50 %), the median T_{max} was later (by approximately 20 hrs), and the mean half-lives were longer (by approximately 2- to 4 fold) than in healthy volunteers (see **Contraindications**).

Elderly:

Pharmacokinetic studies have shown variable results. A single dose study showed that the pharmacokinetics of bupropion and its metabolites in the elderly are not different from those in the younger adults.
Another pharmacokinetic study, single and multiple dose, suggested that accumulation of bupropion and its metabolites may occur to a greater extent in elderly subjects.
Clinical experience did not identify differences in tolerability between older and younger patients, but greater sensitivity in the elderly cannot be ruled out.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Colloidal silicon dioxide

Hydrochloric acid

Hydroxypropylcellulose

Magnesium stearate

Microcrystalline cellulose

Stearic acid

Colourant:

Light green Opadry II (40L 11438)

Clear aqueous film-coating solution:

Clear Opadry YS-1-7006

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.

Keep the bottle well closed.

Keep out of reach and sight of children.

6.5. Nature and contents of container:

DIRENTO SR 150 mg *60's* will be packed using a 120 ml round, beige, opaque high-density polyethylene (HDPE) bottle with a 38 mm beige plastic child-resistant closure with a tamper evident inner seal, bonded to a white lined pulp board liner. Three 2 gm, 2 in 1 combination canister desiccants are employed.

DIRENTO SR 150 mg *100's* will be packed using a 150 ml round, beige, opaque high-density polyethylene (HDPE) bottle with a 38 mm beige plastic child-resistant closure with a tamper evident inner seal, bonded to a white lined pulp board liner. Three 2 gm, 2 in 1 combination canister desiccants are employed.

DIRENTO SR 150 mg *500's* will be packed using a 532,26 ml oblong, beige, opaque high-density polyethylene (HDPE) bottle, with a 53 mm beige fine ribbed plastic child- resistant closure with a tamper evident inner seal, bonded to a white lined pulp board liner.

Five 6 gm, 2 in 1 packet desiccants are employed.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

TRINITY PHARMA (PTY) LTD.

106 16th Road, Building 2,

Midrand,

1686,

South Africa

8. REGISTRATION NUMBER(S):

DIRENTO SR 150 mg: 45/1.2/0826

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

31 July 2014

10. DATE OF REVISION OF THE TEXT:

2 May 2023