Product Summary

1. Name of the medicinal product
Cognix Plus®

2. Qualitative and quantitative composition
Each film coated tablet contains
Piracetam BP 800 mg
Ginkgo biloba extract 60 mg
Vinpocetine 5mg

3. Pharmaceutical form
Film coated tablet

4. Clinical particulars
4.1 Therapeutic indications

Piracetam
1. Studies carried out in the elderly suffering from loss of memory, vertigo, a lack of concentration or of alertness, changes of mood, a deterioration in behaviour and personal negligence, demonstrate an improvement in symptoms. These symptoms can also provide an early warning of the onset of pathological ageing such as Alzheimer's Disease, an Alzheimer type of senile dementia, or the dementia produced by multiple cerebral infarcts.

2. Piracetam is advocated in the treatment of sickle-cell vaso-occlusive crises.

3. Studies have shown some improvement in children with learning difficulties associated with the written word, particularly with textual understanding which cannot be explained by intellectual backwardness, inadequate education or by the family environment. The administration of piracetam does not replace other measures also well adapted to correct these learning difficulties, such as remedial teaching.
**Ginkgo biloba**
A traditional herbal medicinal product used to relieve the symptoms of Raynaud’s syndrome and tinnitus, based on traditional use only.

**Vinpocetine**
The primary claim made for vinpocetine is that it decreases fatality and dependency in ischemic stroke. Research results are mixed. Vinpocetine has not been helpful in Alzheimer's disease, but there is some suggestion that it might help some with other dementias and cerebral dysfunction. Very preliminary research additionally suggests that vinpocetine may help protect the eye and ear from injuries caused by trauma (and, in the case of the eye, from infection) and that it might be gastro-protective, ameliorate symptoms of motion sickness and help prevent atherosclerosis.

### 4.2 Posology and method of administration
Cognix Plus® should be used as prescribed by the physician. The recommendations for the various components are as follows.

**Piracetam** should be administered orally, and may be taken with or without food. The film-coated tablets should be swallowed with liquid.

- The total daily dose can range from 30 to 160 mg/kg/day depending on the indication. This is administered twice daily, but may also be given in three or four separate doses. When treating severe symptoms, 12 g daily may need to be administered as an intravenous infusion.
- Piracetam, as a long-term therapy for psycho-organic syndrome in the elderly is given in doses ranging from 1.2 to 2.4 g daily, according to the severity of the symptoms. The loading dose can be as high as 4.8 g/day during the initial weeks of treatment.
- When treating sickle-cell vaso-occlusive crises, the dose administered is 160 mg/kg/day divided in four equal doses.
- In the treatment of 8 to 13 year-old children with learning difficulties piracetam is given at a total dose of 3.3 g daily. This is administered either as 8 ml of a 20% solution or 5 ml of a 33% solution twice a day i.e. before breakfast and before the evening meal. The medication may be more easily accepted if given in fruit
juice, or in some other drink. Treatment should be continued throughout the school year. The efficacy of a longer period of treatment has not yet been investigated. Elderly Adjustment of the dose is recommended in elderly patients with compromised renal function (see Sections: Warnings and Precautions; Renal Impairment below). For long term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed.

**Renal impairment**

Piracetam is contraindicated in severe renal impairment (renal creatinine clearance of less than 20 ml per minute) (see Sections: Contraindications; Warnings and Precautions). The daily dose must be individualised according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient’s creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

\[
\text{CLcr} = \frac{[140 \text{ – age (years)}] \times \text{weight (kg)} \times 0.85 \text{ for women}}{72 \times \text{serum creatinine (mg/dl)}}
\]

<table>
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<tr>
<th>Group</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Posology and frequency</th>
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<tr>
<td>Normal</td>
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<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>1/6 usual daily dose, 1 single intake</td>
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<tr>
<td>End-stage renal disease</td>
<td>--</td>
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**Hepatic impairment**

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of dose is recommended (see dose adjustment in Renal Impairment above).

**Ginkgo biloba**

Adults and the elderly: As prescribed by the physician

Children and adolescents less than 18 years old:

The use in children and adolescents under 18 years of age is not recommended (see Section 4.4).

Duration of use: If the symptoms worsen or persist for more than 4 weeks a doctor or
a qualified healthcare practitioner should be consulted.

**Vinpocetine**

This is available as an individual supplement and in combination products. Typical doses for supplement use are 5 to 10 milligrams daily with food. Some take up to 20 milligrams daily. Higher doses are not advised. Caution must be exercised before starting to take this medicine. It is vital that doctor should be consulted.

### 4.3 Contraindications

**Piracetam** is contraindicated in:

- Hypersensitivity to piracetam, other pyrrolidone derivatives or any of the excipients;
- Patients with end-stage renal disease (renal creatinine clearance of less than 20 ml per minute);
- Patients with cerebral haemorrhage;
- Patients suffering from Huntington's Chorea.

Do not use in cases of known hypersensitivity to Ginkgo preparations or to any of the excipients.

### 4.4 Special warnings and precautions for use

**Piracetam**

*Effects on platelet aggregation*

Due to the effect of piracetam on platelet aggregation, caution is recommended in patients with severe haemorrhage, patients at risk of bleeding such as gastrointestinal ulcer, patients with underlying disorders of haemostasis, patients with history of haemorrhagic CVA, patients undergoing major surgery including dental surgery, and patients using anticoagulants or platelet antiaggregant drugs including low dose aspirin.

*Renal insufficiency*

Piracetam is eliminated via the kidneys and care should thus be taken in cases of renal insufficiency (see Section: Dosage and Administration).
Elderly
For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed (see Section: Dosage and Administration).

Discontinuation
Abrupt discontinuation of treatment should be avoided as this may induce myoclonic or generalised seizures in some myoclonic patients.

Sickle-cell vaso-occlusive crises
For sickle-cell indication, a dose lower than 160 mg/kg/day or irregular intake may result in relapse of crises.

Ginkgo biloba
The use in children and adolescents under 18 years of age is not recommended because data are not sufficient and medical advice should be sought. Keep out of the reach and sight of children.
There are rare case reports of spontaneous bleeding in association with the use of products containing Ginkgo extracts. Although no causal link has been established care should be taken by patients who have a pre-existing bleeding disorder. It is advisable that Ginkgo is discontinued at least 2 weeks prior to surgery or that clotting parameters are assessed prior to surgery.

Vinpocetine
Those with a history of allergic reactions or hypersensitivity reactions during treatment with other vinca alkaloids, such as vinblastine and vincristine, should avoid vinpocetine. Those on warfarin are advised to have their INRs (international normalized ratios) regularly monitored when using vinpocetine supplements (see Interactions). Those with hypotension or orthostatic hypotension should be cautioned that prolonged use of vinpocetine may lead to slight reductions in systolic and diastolic blood pressure.
4.5 Interaction with other medicinal products and other forms of interaction

**Piracetam**

Pharmacokinetic interactions

The drug interaction potential resulting in changes of piracetam pharmacokinetics is expected to be low because approximately 90% of the dose of piracetam is excreted in the urine as unchanged drug.

In vitro, piracetam does not inhibit the human liver cytochrome P450 isoforms CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A9/11 at concentrations of 142, 426 and 1422 μg/ml. At 1422 μg/ml, minor inhibitory effects on CYP 2A6 (21%) and 3A4/5 (11%) were observed. However, the Ki values for inhibition of these two CYP isoforms are likely to be well in excess of 1422 μg/ml.

Therefore, metabolic interaction of piracetam with other drugs is unlikely.

**Thyroid hormones**

Confusion, irritability and sleep disorder have been reported during concomitant treatment with thyroid extract (T3 + T4).

**Acenocoumarol**

In a published single-blind study on patients with severe recurrent venous thrombosis, piracetam 9.6 g/d did not modify the doses of acenocoumarol necessary to reach INR 2.5 to 3.5, but compared with the effects of acenocoumarol alone, the addition of piracetam 9.6 g/d significantly decreased platelet aggregation, β-thromboglobulin release, levels of fibrinogen and von Willebrand's factors (VIII: C; VIII: vW: Ag; VIII: vW: RCo) and whole blood and plasma viscosity.

**Antiepileptic drugs**

A 20 g daily dose of piracetam over 4 weeks did not modify the peak and trough serum levels of antiepileptic drugs (carbamazepine, phenytoin, phenobarbitone, valproate) in epileptic patients who were receiving stable doses.

Appropriate studies have not been conducted to determine whether drug interactions occur with Ginkgo and its active constituents.

**Vinpocetine**

Warfarin — Slight changes in prothrombin time have been noted in those adding
vinpocetine to warfarin dosing. The changes appear minimal. However, regular monitoring of INR is advised in those using warfarin and vinpocetine concomitantly. There are no other known drug or nutritional supplement, herb or food interactions.

4.6 Fertility, Pregnancy and lactation

**Fertility**
There are no relevant data available.

**Pregnancy**
Piracetam should not be used during pregnancy unless clearly necessary, when benefit exceeds the risks and the clinical condition of the pregnant mother requires treatment with piracetam.

There are no adequate data from the use of piracetam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development.

Piracetam crosses the placental barrier. Drug levels in the newborn are approximately 70% to 90% of maternal levels.

**Lactation**
Piracetam should not be used during breast-feeding or breast-feeding should be discontinued, while receiving treatment with piracetam. A decision must be made whether to discontinue breast-feeding or to discontinue piracetam therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Piracetam is excreted in human breast milk.

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

**Vinpocetine**
Pregnant women and nursing mothers should avoid vinpocetine supplements.

4.7 Effects on ability to drive and use machines

In view of the undesirable side effects, which were observed after the administration of the preparation, there is the possibility of influence on the ability to drive and to operate machinery and this should be taken into consideration.
### 4.8 Undesirable effects

**Piracetam**

Clinical studies

Double-blind placebo-controlled clinical or pharmaco-clinical trials, of which quantified safety data are available (extracted from the UCB Documentation Data Bank on June 1997), included more than 3000 subjects receiving piracetam, regardless of indication, dosage form, daily dosage or population characteristics. Frequencies are defined as follows: very common: $\geq$1/10; common $\geq$1/100, <1/10; uncommon $\geq$1/1,000, <1/100; rare $\geq$1/10,000, <1/1,000; very rare <1/10,000 and not known (cannot be estimated from the available data).

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**Ginkgo biloba**

The following adverse reactions have rarely been reported in association with the use of products containing Gingko extract.

Body as a whole – general disorders

- Allergy

Central and peripheral nervous system disorders

- Headache

Gastrointestinal system disorders

- Nausea
- Vomiting
- Diarrhoea

Skin and appendages

- Pruritus
- Rash

There have been very rare case reports of Stevens-Johnson syndrome associated with the use of Ginkgo extract.

There are sporadic case reports of bleeding disorders in patients who have been taking preparations containing Ginkgo extract. The causality in these cases is not established.

**Vinpocetine**

Reported adverse reactions include nausea, dizziness, insomnia, drowsiness, dry mouth, transient hypotension, transient tachycardia, pressure-type headache and facial flushing. Slight reductions in both systolic and diastolic blood pressure with prolonged use of vinpocetine have been reported, as well as slight reductions in blood glucose.

**4.9 Overdose**

Symptoms and signs

No additional adverse events specifically related to overdose have been reported with piracetam.

The highest reported overdose with piracetam was oral intake of 75 g wherein bloody diarrhoea with abdominal pain, was most probably related to the extreme
high dose of sorbitol contained in the used formulation. There are no reports of vinpocetine overdosage.

5. Pharmacological properties
5.1 Pharmacodynamic properties

**Piracetam**

**Pharmacotherapeutic group**
Psychostimulants, agents used for ADHD and nootropics.

**Mechanism of Action**
Available data suggest that piracetam basic mechanism of action is neither cell- nor organ-specific. Piracetam binds physically in a dose-dependent manner to the polar head of phospholipids membrane models, inducing the restoration of the membrane lamellar structure characterised by the formation of mobile drug-phospholipid complexes. This probably accounts for an improved membrane stability, allowing the membrane and transmembrane proteins to maintain or recover the three-dimensional structure or folding essential to exert their function. Piracetam has neuronal and vascular effects.

**Pharmacodynamic effects**

**Neuronal effect**
At the neuronal level, piracetam exerts its membrane activity in various ways. In animals, piracetam enhances a variety of types of neurotransmission, primarily through postsynaptic modulation of receptor density and activity. In both animals and man, the functions involved in cognitive processes such as learning, memory, attention and consciousness were enhanced, in the normal subject as well as in deficiency states, without the development of sedative or psychostimulant effects. Piracetam protects and restores cognitive abilities in animals and man after various cerebral insults such as hypoxia, intoxications and electroconvulsive therapy. It protects against hypoxia-induced changes in brain function and performance as assessed by electroencephalograph (EEG) and psychometric evaluations.

**Vascular effects**
Piracetam applies its haemorrhagic effect to thrombocytes, erythrocytes and the walls of the blood vessels by increasing the deformability of erythrocytes, reducing the aggregability of thrombocytes, reduces the adhesion of erythrocytes to the walls
of vessels and reduces capillary vasospasm.

**Effects on the red blood cells**

In patients with sickle-cell anaemia, piracetam improves the deformability of the erythrocyte membrane, decreases blood viscosity and prevents rouleaux formation.

**Effects on platelets**

In open studies in healthy volunteers and in patients with Raynaud’s phenomenon, increasing doses of piracetam up to 12 g was associated with a dose-dependent reduction in platelet functions compared with pre-treatment values (tests of aggregation induced by ADP, collagen, epinephrine and β TG release), without significant change in platelet count. In these studies, piracetam prolonged bleeding time.

**Effects on blood vessels**

In animal studies, piracetam inhibited vasospasm and counteracted the effects of various spasmogenic agents. It lacked any vasodilatory action and did not induce “steal” phenomenon, nor low or no reflow, nor hypotensive effects.

In healthy volunteers, piracetam reduced the adhesion of RBCs to vascular endothelium and possessed also a direct stimulant effect on prostacycline synthesis in healthy endothelium.

**Effects on coagulation factors:** In healthy volunteers, compared with pre-treatment values, piracetam up to 9.6 g reduced plasma levels of fibrinogen and von Willebrand’s factors (VIII: C; VIII R: AG; VIII R: vW) by 30 to 40%, and increased bleeding time.

In patients with both primary and secondary Raynaud’s phenomenon, compared with pretreatment values, piracetam 8 g/d during 6 months reduced plasma levels of fibrinogen and von Willebrand’s factors (VIII: C; VIII R: AG; VIII R: vW (RCF)) by 30 to 40%, reduced plasma viscosity, and increased bleeding time.

**Ginkgo biloba**

No information is available

**Vinpocetine**

Vinpocetine has several possible actions, including increasing cerebral blood flow and metabolism, anticonvulsant, cognition enhancement, neuroprotection and antioxidant. Vincamine, the parent compound of vinpocetine, is believed to be a
Several small studies, in both animals and humans, have reported significant vinpocetine-associated protective effects in ischemic stroke. A review of these studies, however, found only one positive study of a truly randomized, unconfounded clinical trials that compared the effect of vinpocetine to either placebo or another reference treatment for acute stroke where treatment started no later than 14 days after stroke onset. There is currently not enough evidence to determine whether vinpocetine does or does not reduce fatalities and dependence in ischemic stroke. Further research is needed. There is some evidence vinpocetine may be useful in some other cerebral maladies. In one multi-center, double-blind, placebo-controlled study lasting 16 weeks, 203 patients described as having mild to moderate psycho-syndromes, including primary dementia, were treated with varying doses of vinpocetine or placebo. Significant improvement was achieved in the vinpocetine-treated group as measured by "global improvement" and cognitive performance scales. Three 10-milligram doses daily were as effective or more effective than three 20-milligram doses daily. Similarly, good results were found in another double-blind clinical trial testing vinpocetine versus placebo in elderly patients with cerebrovascular and central nervous system degenerative disorders. Studies of Alzheimer's disease, however, have shown no vinpocetine benefit. Some preliminary research suggests that vinpocetine may have some protective effects in both sight and hearing. One study of patients with mild burn trauma in the eyes showed that vinpocetine enhanced healing, most likely as a result of increased blood flow to the damaged tissue. Vinpocetine has also been associated with improvements seen in retinas damaged by hepatitis B virus. Damage from acoustic trauma has similarly been reduced by vinpocetine treatment. Vinpocetine gastroprotective effects have been reported in animal models challenged with noxious agents. There are anecdotal reports that vinpocetine is protective against some of the gastric and neurological toxicity of excessive alcohol consumption. There are some reports that vinpocetine may be an effective motion sickness preventative and some early findings in animals that it may exert some anti-atherosclerotic effects through a reported ability to decalcify cholesterol-induced atherosclerotic lesions.

Mechanism of action:
Several mechanisms have been proposed for the possible actions of vinpocetine.
Vinpocetine has been reported to have calcium-channel blocking activity, as well as voltage-gated sodium channel blocking activity. It has also been reported to inhibit the acetylcholine release evoked by excitatory amino acids and to protect neurons against excitotoxicity. In addition, vinpocetine has been shown to inhibit a cyclic GMP phosphodiesterase, and it is speculated that this inhibition enhances cyclic GMP levels in the vascular smooth muscle, leading to reduced resistance of cerebral vessels and increase of cerebral flow. In some studies, vinpocetine has demonstrated antioxidant activity equivalent to that of vitamin E.

5.2 Pharmacokinetic properties

*Piracetam*

The pharmacokinetic profile of piracetam is linear and time-independent with low inter-subject variability over a large range of doses. This is consistent with the high permeability, high solubility and minimal metabolism of piracetam. Plasma half-life of piracetam is 5 hours. It is similar in adult volunteers and in patients. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment. Steady state plasma concentrations are achieved within 3 days of dosing.

*Absorption*

Piracetam is rapidly and extensively absorbed following oral administration. In fasted subjects, the peak plasma concentrations are achieved 1 hour after dosing. The absolute bioavailability of piracetam oral formulations is close to 100%. Food does not affect the extent of absorption of piracetam but it decreases $C_{\text{max}}$ by 17% and increases $T_{\text{max}}$ from 1 to 1.5 hours. Peak concentrations are typically 84 μg/ml and 115 μg/ml following a single oral dose of 3.2 g and repeat dose of 3.2 g t.i.d. respectively.

*Distribution*

Piracetam is not bound to plasma proteins and its volume of distribution is approximately 0.6 l/kg. Piracetam crosses the blood brain barrier as it has been measured in cerebrospinal fluid following intravenous administration. In cerebrospinal fluid, the $T_{\text{max}}$ was achieved about 5 hours post-dose and the half-life was about 8.5 hours. In animals, piracetam highest concentrations in the brain were in the cerebral cortex (frontal, parietal and occipital lobes), in the cerebellar cortex and in the basal ganglia. Piracetam diffuses to all tissues except adipose tissues,
crosses placental barrier and penetrates the membranes of isolated red blood cells.

**Metabolism**

Piracetam is not known to be metabolised in the human body. This lack of metabolism is supported by the lengthy plasma half-life in anuric patients and the high recovery of parent compound in urine.

**Elimination**

The plasma half-life of piracetam in adults is about 5 hours following either intravenous or oral administration. The apparent total body clearance is 80-90 ml/min. The major route of excretion is via urine, accounting for 80 to 100% of the dose. Piracetam is excreted by glomerular filtration.

**Linearity**

The pharmacokinetics of piracetam are linear over the dose range of 0.8 to 12 g. Pharmacokinetic variables like half-life and clearance are not changed with respect to the dose and the duration of treatment.

**Special patient populations**

Children: No formal pharmacokinetic study has been conducted in children.

Elderly: In the elderly, the half-life of piracetam is increased and the increase is related to the decrease in renal function in this population (see Section Dosage and Administration).

**Renal impairment**

Piracetam clearance is correlated to creatinine clearance. It is therefore recommended to adjust the daily dose of piracetam based on creatinine clearance in patients with renal impairment (see Section Dosage and Administration).

**Hepatic impairment**

The influence of hepatic impairment on the pharmacokinetics of piracetam has not been evaluated. Because 80 to 100% of the dose is excreted in the urine as unchanged drug, hepatic impairment solely would not be expected to have a significant effect on piracetam elimination.

Other patient characteristics
Race
Formal pharmacokinetic studies of the effects of race have not been conducted. Because piracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies
See Section Pharmacodynamic effects

Ginkgo biloba
No information is available

Vinpocetine
Vinpocetine is absorbed from the small intestine, from whence it is transported to the liver via the portal circulation. From the liver via the systemic circulation, it is distributed to various tissues in the body, including the brain. Absorption of vinpocetine is significantly higher when given with food and can be up to about 60% of an ingested dose. On an empty stomach, absorption of an ingested dose can be as low as 7%. Peak plasma levels are obtained one to one and a half hours after ingestion. Extensive metabolism to the inactive apovincaminic acid occurs in the liver. Only small amounts of unmetabolized vinpocetine are excreted in the urine, the major route of excretion of apovincaminic acid. Most of a dose is excreted within 24 hours as this metabolite. The elimination half-life of vinpocetine following ingestion is one to two hours.

5.3 Preclinical safety data
Piracetam
Single doses of piracetam yielded LD$_{50}$ values at 26 g/kg in mice but LD$_{50}$ values were not reached in rats. In dogs, clinical signs after acute oral dosing were mild and lethality was not observed at the maximum tested dose of 10 g/kg. Repeated oral treatment for up to 1 year in dogs (10 g/kg) and 6 months in rats (2 g/kg) was very well tolerated: no target organ toxicity or signs of (irreversible) toxicity were clearly demonstrated. Safe dose levels represent a multiple of the maximum intended human daily dose of 0.4 g/kg.
In terms of exposure ($C_{\text{max}}$) safe levels obtained in the rat and the dog represent respectively 8 fold and 50 fold of the maximum human therapeutic level. AUC levels obtained in the same animals were a multiple of the human AUC level at the maximum intended daily dose.

The only change which might eventually be attributed to chronic treatment in male, but not in female, rats was an increase of the incidence over control animals of progressive glomerulo-nephrosis at the dose of 2.4 g/kg/day given for 112 weeks. Although piracetam crosses the placenta into the foetal circulation, no teratogenic effects were observed at dose levels up to 4.8 g/kg/day (mice, rats) and 2.7 g/kg/day (rabbits). Furthermore, the compound affects neither fertility nor the peri- or postnatal development of the pregnancy at doses up to 2.7 g/kg/day.

Piracetam was found to be devoid of any mutagenic or clastogenic activity and does not represent any genotoxic or carcinogenic risk to man.

**Ginkgo biloba**

The preclinical toxicology data available are limited. An in vitro study has shown the aqueous ethanolic Ginkgo extract used in this product to be non-mutagenic in the Salmonella typhimurium reverse mutation assay up to the dose of 5,000 μg/plate. Tests on reproductive toxicity and carcinogenicity have not been performed.

No data is available for **vinpocetine**

### 6. Pharmaceutical particulars

**6.1 List of excipients**

Titanium dioxide

**6.2 Incompatibilities**

Not known

**6.3 Shelf life**

24 months

**6.4 Special precautions for storage**

Store in a cool dry place, protect from light
Administrative data

7. Marketing authorisation holder
Strides Shasun Limited
Strides House, Bilekahalli,
Bannerghatta Road,
Bengaluru – 560 076, India

8. Toll free number for reporting
1800 4190601

9. Date of text
16\textsuperscript{th} May 2016