Tapento® *IR*
(Tapentadol HCl)

1. NAME OF THE PRODUCT
Tapento® *IR* (Tapentadol HCl) 50mg Tablet
Tapento® *IR* (Tapentadol HCl) 75mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tapento® *IR* 50mg Tablet
Each film coated tablet contains:
Tapentadol Hydrochloride MS eq. to Tapentadol.....50mg

Tapento® *IR* 75mg Tablet
Each film coated tablet contains:
Tapentadol Hydrochloride MS eq. to Tapentadol.....75mg

3. PHARMACEUTICAL FORM
Film-coated tablet

Appearance:
Tapento® *IR* 50mg Tablet: Green color round shaped tablet, plain from both sides.
Tapento® *IR* 75mg Tablet: Yellow color capsular tablet with SAMI engraved on one side and break line on other side.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Tapento® *IR* is indicated for the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
The dosing regimen should be individualized according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.
Patients should start treatment with single doses of 50 mg tapentadol as film-coated tablet administered every 4 to 6 hours. Higher starting doses may be necessary depending on the pain intensity and the patient's previous history of analgesic requirements.
On the first day of dosing, an additional dose may be taken as soon as one hour after the initial dose, if pain control is not achieved. The dose should then be

titrated individually to a level that provides adequate analgesia and minimises undesirable effects under the close supervision of the prescribing physician.
Total daily doses greater than 700mg **Tapento® IR** on the first day of treatment and maintenance daily doses greater than 600mg **Tapento® IR** have not been studied and are therefore not recommended.
Duration of treatment: Tapento® IR should not be used longer than necessary. The film-coated tablets are intended for acute pain situations. If longer term treatment is anticipated or becomes necessary and effective pain relief in the absence of intolerable adverse events was achieved with tapentadol, the possibility of switching the patient to therapy with tapentadol prolonged release tablets should be considered. As with all symptomatic treatments, the continued use of tapentadol must be evaluated on an ongoing basis.
Renal Impairment: In patients with mild or moderate renal impairment a dosage adjustment is not required. Tapentadol has not been studied in controlled efficacy trials in patients with severe renal impairment, therefore the use in this population is not recommended.
Hepatic impairment: In patients with mild hepatic impairment a dosage adjustment is not required. **Tapento® IR** should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at the lowest available dose strength, i.e., 50mg tapentadol as film coated tablet, and not be administered more frequently than once every 8 hours. At initiation of therapy a daily dose greater than 150mg tapentadol as film-coated tablet is not recommended. Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval.
Tapentadol has not been studied in patients with severe hepatic impairment and therefore, use in this population is not recommended.
Elderly patients (persons aged 65 years and over): In general, a dose adaptation in elderly patients is not required. However, as elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended.
Paediatric population: The safety and efficacy of this medicine in children and adolescents below 18 years of age has not yet been established. Therefore, tapentadol is not recommended for use in this population.

Method of administration:
For oral use.
This medicine should be taken with sufficient liquid. **Tapento® IR** can be taken with or without food.
Treatment goals and discontinuation: Before initiating treatment with tapentadol, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment,

there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tapentadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients.
- In situations where active substances with mu-opioid receptor agonist activity are contraindicated, i.e., patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercapnia.
- In any patient who has or is suspected of having paralytic ileus.
- In patients with acute intoxication with alcohol, hypnotics, centrally acting analgesics, or psychotropic active substances.

4.4. SPECIAL WARNING AND PRECAUTIONS FOR USE:

Tolerance and Opioid Use Disorder (abuse and dependence): Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as tapentadol. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders). Before initiating treatment with tapentadol and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient. Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician. Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Risk from concomitant use of sedating medicinal products such as benzodiazepines or related substances: Concomitant use of tapentadol and sedating medicinal products such as benzodiazepines or related substances may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products

should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe this medicine concomitantly with sedating medicinal products, the reduction of dose of one or both agents should be considered, and the duration of the concomitant treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms.

Respiratory Depression: At high doses or in mu-opioid receptor agonist sensitive patients, tapentadol may produce dose-related respiratory depression. Therefore, this medicine should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor agonist analgesics should be considered and this medicine should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid receptor agonist-induced respiratory depression.

Head Injury and Increased Intracranial Pressure: Tapentadol should not be used in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Analgesics with mu-opioid receptor agonist activity may obscure the clinical course of patients with head injury. This medicine should be used with caution in patients with head injury and brain tumors.

Seizures: Like other analgesics with mu-opioid agonist activity tapentadol is not recommended in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures. In addition, tapentadol may increase the seizure risk in patients taking other medicinal products that lower the seizure threshold.

Renal Impairment: The use of tapentadol is not recommended in patients with severe renal impairment.

Hepatic Impairment: Tapentadol should be used with caution in patients with moderate hepatic impairment, especially upon initiation of treatment. Tapentadol is not recommended in patients with hepatic impairment.

Use in Pancreatic/Biliary Tract Disease: Active substances with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. This medicine should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Sleep-related breathing disorders: Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Mixed opioid agonists/antagonists: Care should be taken when combining Tapentadol with mixed mu-opioid agonist/antagonists (like pentazocine, nalbuphine) or partial mu-opioid agonists (like buprenorphine). In patients

maintained on buprenorphine for the treatment of opioid dependence, alternative treatment options (like e.g., temporary buprenorphine discontinuation) should be considered, if administration of full mu-agonists (like tapentadol) becomes necessary in acute pain situations. On combined use with buprenorphine, higher dose requirements for full mu-receptor agonists have been reported and close monitoring of adverse events such as respiratory depression is required in such circumstances.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Centrally-acting medical products/central nervous system (CNS) depressants, including alcohol and CNS depressant narcotic drugs: The concomitant use of tapentadol with sedating medicinal products such as benzodiazepines or other respiratory or CNS depressants (other opioids, antitussives or substitution treatments, barbiturates, antipsychotics, H1-antihistamines, alcohol) increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Therefore, when a combined therapy with a respiratory or CNS depressant is contemplated, the reduction of dose of one or both agents should be considered and the duration of the concomitant use should be limited. The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Mixed opioid agonists/antagonists: Care should be taken when combining with mixed mu-opioid agonist/antagonists (like pentazocine, nalbuphine) or partial mu-opioid agonists (like buprenorphine). Tapentadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other medicinal products that lower the seizure threshold to cause convulsions. There have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tapentadol in combination with serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants.

Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38°C and inducible ocular clonus.

Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms. The major elimination pathway for tapentadol is conjugation with glucuronic acid mediated via uridine diphosphate transferase (UGT) mainly UGT1A6, UGT1A9 and UGT2B7 isoforms. Thus, concomitant administration with strong inhibitors of these isoenzymes (e.g., Ketoconazole, fluconazole, meclofenamic acid) may lead to increased systemic exposure of tapentadol.

For patients on tapentadol treatment, caution should be exercised if concomitant drug administration of strong enzyme inducing drugs (e.g., rifampicin, phenobarbital, St John's Wort (Hypericum perforatum)) starts or stops, since this may lead to decreased efficacy or risk for adverse effects, respectively.

Treatment with tapentadol should be avoided in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on synaptic noradrenaline concentrations which may result in adverse cardiovascular events, such as hypertensive crisis.

Anticholinergics: Concomitant administration of tapentadol with anticholinergics or medications with anticholinergic activity (e.g., tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: No human data on the effect of tapentadol on fertility are available.

Pregnancy: There is very limited amount of data from the use in pregnant women. This medicine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Delayed development and embryotoxicity were observed at doses resulting in exaggerated pharmacology (mu-opioid-related CNS effects related to dosing above the therapeutic range). Effects on the postnatal development were already observed at the maternal NOAEL Long-term maternal use of opioids during pregnancy co-exposes the fetus. The new-born may experience subsequent neonatal withdrawal syndrome (NOWS). Neonatal opioid withdrawal syndrome can be life-threatening if not recognised and treated. An antidote for the newborn should be readily available.

Labour and delivery: The effect of tapentadol on labour and delivery in humans is unknown. This medicine is not recommended for use in women during and immediately before labour and delivery. Due to the mu-opioid receptor agonist activity of tapentadol, new-born infants whose mothers have been taking tapentadol should be monitored for respiratory depression.

Breast-feeding: There is no information on the excretion of tapentadol in human milk. Tapentadol should not be used during breast-feeding.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Tapentadol may have major influence on the ability to drive and use machines, because it may adversely affect central nervous system functions. This has to be expected especially at the beginning of treatment, when any changes of dosage occur as well as in connection with the use of alcohol or tranquilisers. Patients should be cautioned as to whether driving or use of machines is permitted.

4.8. UNDESIRABLE EFFECTS:

The adverse drug reactions are listed by class and frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune system disorders:

Rare: Drug hypersensitivity*

Metabolism and nutrition disorders:

Common: Decreased appetite

Psychaiatric disorders:

Common: Anxiety, confusional state, hallucination, sleep disorder, abnormal dreams

Uncommon: Depressed mood, disorientation, agitation, nervousness, restlessness, euphoric mood, drug dependence

Rare: Thinking abnormal

Not Known: Delirium **

Nervous System disorders:

Very common: Dizziness, somnolence, headache

Common: Tremor

Uncommon: disturbance in attention, memory impairment, presyncope, sedation, ataxia, dysarthria, hypoaesthesia, paraesthesia, muscle contractions involuntary

Rare: Convulsion, depressed level of consciousness, coordination abnormal

Eye disorders:

Uncommon: Visual disturbance

Cardiac disorders:

Uncommon: Heart rate increased, palpitations

Rare: Heart rate decreased

Vascular disorders:

Common: Flushing

Uncommon: Blood pressure decreased

Respiratory, thoracic and mediastinal disorders:

Uncommon: Respiratory depression, oxygen saturation decreased, dyspnoea

Gastrointestinal disorder:

Very Common: Nausea, vomiting

Common: Constipation, diarrhoea, dyspepsia, dry mouth
Uncommon: Abdominal discomfort
Rare: Impaired gastric emptying
Skin and subcutaneous tissue disorder:
Common: Pruritus, hyperhidrosis, rash
Uncommon: Urticaria
Musculoskeletal and connective tissue disorder:
Common: Muscle spasms
Uncommon: Sensation of heaviness
Renal and urinary disorders:
Uncommon: Urinary hesitation, pollakiuria
General disorders and administration site conditions:
Common: Asthenia, fatigue, feeling of body temperature change
Uncommon: Drug withdrawal syndrome, oedema, feeling abnormal, feeling drunk, irritability, feeling of relaxation
*Post-marketing rare events of angioedema, anaphylaxis and anaphylactic shock have been reported.
**Post marketing cases of delirium were observed in patients with additional risk factors such as cancer and advanced age.
The risk of suicidal ideation and suicides committed is known to be higher in patients suffering from chronic pain. In addition, substances with a pronounced influence on the monoaminergic system have been associated with an increased risk of suicidality in patients suffering from depression, especially at the beginning of treatment.

4.9. OVERDOSE:

Symptoms: Human experience with overdose of tapentadol is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid receptor agonist activity are to be expected upon intoxication with tapentadol. In principle, these symptoms include, referring to the clinical setting, in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest that may be fatal.
Management: Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of tapentadol is suspected. Pure opioid receptor antagonists such as naloxone are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid receptor antagonist. Administration of an opioid receptor antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid receptor antagonists is suboptimal or only brief in nature,

an additional dose of antagonist (e.g., naloxone) should be administered as directed by the manufacturer of the product. Gastrointestinal decontamination may be considered in order to eliminate unabsorbed active substance. Gastrointestinal decontamination with activated charcoal or by gastric lavage may be considered within 2 hours after intake. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Analgesics; opioids; other opioids.

ATC code: N02AX06

Mechanism of Action:

Tapentadol is a strong analgesic with μ-agonistic opioid and additional noradrenaline reuptake inhibition properties. Tapentadol exerts its analgesic effects directly without a pharmacologically active metabolite.

5.2. PHARMACOKINETIC PROPERTIES:

Absorption: Tapentadol is rapidly and completely absorbed after oral administration of tapentadol. Mean absolute bioavailability after single-dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after administration of film-coated tablets. Dose-proportional increases in the C_{max} and AUC values of tapentadol have been observed after administration of film-coated tablets over the oral therapeutic dose range.

Food Effect: The AUC and C_{max} increased by 25% and 16%, respectively, when film-coated tablets were administered after a high-fat, high-calorie breakfast. The time to maximum plasma concentration was delayed by 1.5 hours under these conditions. Tapentadol may be given with or without food.

Distribution: Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution (Vz) for tapentadol is 540±98 l. The serum protein binding is low and amounts to approximately 20%.

Metabolism: In humans, the metabolism of tapentadol is extensive. About 97% of the parent compound is metabolised. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% of the dose is excreted in urine as conjugated forms (55% glucuronide and 15% sulfate of tapentadol). Uridine diphosphate glucuronyl transferase (UGT) is the primary enzyme involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). A total of 3% of active substance is excreted in urine as unchanged active substance. Tapentadol is additionally metabolised to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolised by conjugation. Therefore, active substance metabolism

mediated by cytochrome P450 system is of less importance than glucoronidation. None of the metabolites contributes to the analgesic activity.
Elimination: Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The total clearance after intravenous administration is 1530±177ml/min. Terminal half-life is on average 4 hours after oral administration.

5.3. PRECLINICAL SAFETY DATA:

Tapentadol was not genotoxic in bacteria in the Ames test. Equivocal findings were observed in an in vitro chromosomal aberration test, but when the test was repeated the results were clearly negative. Tapentadol was not genotoxic in vivo, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, when tested up to the maximum tolerated dose. Long-term animal studies did not identify a potential carcinogenic risk relevant to humans. Tapentadol had no influence on male or female fertility in rats but there was reduced in utero survival at the high dose. It is not known whether this was mediated via the male or the female. Tapentadol showed no teratogenic effects in rats and rabbits following intravenous and subcutaneous exposure. However, delayed development and embryotoxicity were observed after administration of doses resulting in exaggerated pharmacology (mu-opioid related CNS effects related to dosing above the therapeutic range). After intravenous dosing in rats reduced in utero survival was seen. In rats, tapentadol caused increased mortality of the F1 pups that were directly exposed via milk between days 1 and 4 postpartum already at dosages that did not provoke maternal toxicities. There were no effects on neurobehavioral parameters.
Excretion into breast milk was investigated in rat pups suckled by dams dosed with tapentadol. Pups were dose-dependently exposed to tapentadol and tapentadol O-glucuronide. It was concluded that tapentadol is excreted in milk.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Tapento® *IR* 50mg Tablet:

- Microcrystalline Cellulose
- Lactose Monohydrate
- Crosscarmellose Sodium
- Polyvinyl Pyrrolidone
- Magnesium Stearate
- Purifed Water
- Sheffcoat PVA
- Apple Green Lake Color

Tapento® *IR* 75mg Tablet:

- Microcrystalline Cellulose
- Lactose Monohydrate
- Croscarmellose Sodium
- Polyvinyl Pyrrolidone
- Magnesium Stearate
- Tartrazine Yellow Lake Color
- Purifed Water
- Sheffcoat PVA
- Simethicone LVA

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Tapento® *IR* 50mg Tablet: Alu/Alu blister packing, pack size is 10's.
Tapento® *IR* 75mg Tablet: Alu/Alu blister packing, pack size is 10's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

Tapento® *IR* 50mg Tablet: Innovator's Specs.
Tapento® *IR* 75mg Tablet: Innovator's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

Tapento® IR 50mg Tablet: 109989
Tapento® IR 75mg Tablet: 093064

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Tapento® IR 50mg Tablet: 3rd September, 2021
Tapento® IR 75mg Tablet: 16th January, 2019

10. DATE OF REVISION OF THE TEXT

ٹیپنٹو® آئی آر ٹیبلٹ

(ٹاپینٹاڈول ہائیڈروکلورائیڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری

سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔