01-07-2022
1st Copy

Addition of new strength i.e 50mg

210mm

Tapento® *IR* Tablet

(Tapentadol HCl)

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse: Tapentadol tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing tapentadol tablets, and monitor all patients regularly for the development of these behaviors and conditions. **Life-Threatening Respiratory Depression:** Serious, life-threatening, or fatal respiratory depression may occur with use of tapentadol tablets. Monitor for respiratory depression, especially during initiation of tapentadol tablets or following a dose increase. **Accidental Ingestion:** Accidental ingestion of even one dose of tapentadol tablets, especially by children, can result in a fatal overdose of tapentadol. **Neonatal Opioid Withdrawal Syndrome:** Prolonged use of tapentadol tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants:** Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of tapentadol tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

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

PHARMACEUTICAL FORM

Tablets

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:

Tapento® *IR* (tapentadol hydrochloride) tablets are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults.

Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve **Tapento® *IR*** tablets for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products].

- Have not been tolerated, or are not expected to be tolerated.
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

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. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.
Initiate treatment at a dose of 75mg every 4 to 6 hours depending upon pain intensity. 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 tapentadol on the first day of treatment and maintenance daily doses greater than 600mg tapentadol have not been studied and are therefore not recommended.
Duration of treatment: 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 **Tapento® *IR***. As with all symptomatic treatments, the continued use of tapentadol must be evaluated on an ongoing basis.
Discontinuation of treatment: Withdrawal symptoms could occur after abrupt discontinuation of treatment with tapentadol. When a patient no longer requires therapy with tapentadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.
Paediatric population: The safety and efficacy of **Tapento® *IR*** in children and adolescents below 18 years of age has not yet been established. Therefore, **Tapento® *IR*** is not recommended for use in this population.
Elderly patients: 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.
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.
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.

Method of administration: **Tapento® *IR*** should be taken with sufficient liquid. **Tapento® *IR*** can be taken with or without food.

CONTRAINDICATIONS:

Tapento® *IR* is contraindicated in;

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

SPECIAL WARNING AND PRECAUTIONS FOR USE:

Potential for Abuse and Addiction/Dependence Syndrome: **Tapento® *IR*** has a potential for abuse and addiction. This should be considered when prescribing or dispensing **Tapento® *IR*** in situations where there is concern about an increased risk of misuse, abuse, addiction, or diversion.
All patients treated with active substances that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.
Risk from concomitant use of sedating medicinal products such as benzodiazepines or related substances: Concomitant use of **Tapento® *IR*** 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 **Tapento® *IR*** 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, **Tapento® *IR*** may produce dose-related respiratory depression. Therefore, **Tapento® *IR*** should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor agonist analgesics should be considered and **Tapento® *IR*** 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: **Tapento® *IR*** 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. **Tapento® *IR*** should be used with caution in patients with head injury and brain tumors.
Seizures: **Tapento® *IR*** has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical trials. However, like other analgesics with mu-opioid agonist activity **Tapento® *IR*** 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: **Tapento® *IR*** 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: **Tapento® *IR*** should be used with caution in patients with moderate hepatic impairment, especially upon initiation of treatment. It has not been studied in patients with severe hepatic impairment and therefore, use in this population is not recommended.
Use in Pancreatic / Biliary Tract Disease: Active substances with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. **Tapento® *IR*** should be

120mm

01-07-2022
1st Copy

Addition of new strength i.e 50mg

210mm

used with caution in patients with biliary tract disease, including acute pancreatitis.

Mixed opioid agonists/antagonists: Care should be taken when combining **Tapento®IR** 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.

Tapento®IR tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Sedative medicines such as benzodiazepines or related drugs: The concomitant use of 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.

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) **Tapento®IR** 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 serotonergic 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 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.

PREGNANCY AND LACTATION:

Pregnancy: There is very limited amount of data from the use in pregnant women. **Tapento®IR** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Tapento®IR is not recommended for use in women during and immediately before labor 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. **Tapento®IR** should not be used during breast feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Tapento®IR 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 change of dosage occur as well as in connection with the use of alcohol or tranquilizers. Patients should be cautioned as to whether driving or use of machines is permitted.

UNDESIRABLE EFFECTS:

Gastrointestinal disorders: Diarrhoea.
Nervous system & Psychiatric disorders: Headache, hallucination, suicidal ideation, panic attack.
Cardiac disorders: Palpitations.
Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
Anaphylaxis: Anaphylaxis has been reported with ingredients contained in **Tapento®IR** tablets.
Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids.
The most common reasons for discontinuation due to adverse reactions in the clinical studies were dizziness, nausea, vomiting, somnolence and headache respectively.

OVERDOSE:

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.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Analgesics; opioids; other opioids. **ATC code:** N02AX06

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

PHARMACOKINETIC PROPERTIES:

Absorption: Tapentadol hyrochloride is rapidly and completely absorbed after oral administration of **Tapento®IR** tablets. Mean absolute bioavailability after single-dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol hyrochloride 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 hyrochloride have been observed after administration of film coated tablets over the oral therapeutic dose range.

A multiple (every 6 hour) dose trial with doses ranging from 75 to 175mg tapentadol hyrochloride administered as film coated tablets showed an accumulation ratio between 1.4 and 1.7 for the parent active substance and between 1.7 and 2.0 for the major metabolite tapentadol-O-glucuronide, which are primarily determined by the dosing interval and apparent half-life of tapentadol hyrochloride and its metabolite. Steady state serum concentrations of tapentadol hyrochloride are reached on the second day of the treatment regimen.

Distribution: Tapentadol hyrochloride is widely distributed throughout the body. Following intravenous administration, the volume of distribution for tapentadol hyrochloride is 540+/-98 L. The serum protein binding is low and amounts to approximately 20%.

Metabolism: In humans, the metabolism of tapentadol hyrochloride 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).

Elimination: Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The total clearance after intravenous administration is 1530+/-177 ml/min. Terminal half-life is on average 4 hours after oral administration.

SHELF LIFE

See expiry on the pack.

AVAILABILITY

Tapento®IR 50mg tablet in a pack of 10's.
Tapento®IR 75mg tablet in a pack of 10's.

INSTRUCTIONS

Dosage: As advised by the physician. To be sold on the prescription of registered medical practitioner. Keep out of reach of children.
Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

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

ٹیپنٹو® آئی آر ٹیبلٹ

ٹاپینٹاڈول
(ٹرامیڈول 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۔

2000005147 R.N-04/NA/07/2022

120mm