SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

BUTRUM-2 [Butorphanol Tartrate Injection USP 2 mg]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION :

Each ml contains:
Butorphanol Tartrate USP 2 mg
Sodium Chloride USP 6.4 mg
Suitable buffers added
Water for Injection USP q.s.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

INJECTION

Clear , colourless liquid, filled in 1 ml ampoule having yellow coloured ring and yellow dot printed on it.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Butorphanol Tartrate injection is indicated for the management of pain when the use of an opioid analgesic is appropriate.

Butorphanol Tartrate injection is also indicated as a preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during labor.

4.2 Posology and method of administration:

Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

4. CLINICAL PARTICULARS:

4.2 Posology and method of administration [contd]:

Use for Pain:

Intravenous: The usual recommended single dose for IV administration is 1 mg repeated every 3 to 4 hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 to 2 mg repeated every 3 to 4 hours.

Intramuscular: The usual recommended single dose for IM administration is 2 mg in patients who will be able to remain recumbent, in the event drowsiness or dizziness

occurs. This may be repeated every 3 to 4 hours, as necessary. The effective dosage range depending on the severity of pain is 1 to 4 mg repeated every 3 to 4 hours. There are insufficient clinical data to recommend single doses above 4 mg.

Use as Preoperative/Preanesthetic Medication:

The preoperative medication dosage of Butorphanol Tartrate injection should be individualized .The usual adult dose is 2 mg IM, administered 60-90 minutes before surgery. This is approximately equivalent in sedative effect to 10 mg morphine or 80 mg meperidine.

Use in Balanced Anesthesia:

The usual dose of Butorphanol Tartrate injection is 2 mg IV shortly before induction and/or 0.5 to 1.0 mg IV in increments during anesthesia. The increment may be higher, up to 0.06 mg/kg (4 mg/70 kg), depending on previous sedative, analgesic, and hypnotic drugs administered. The total dose

4.3 Contraindications:

Butorphanol Tartrate injection is contraindicated in patients hypersensitive to Butorphanol Tartrate.

4.4 Special warnings and special precautions for use:

PRECAUTIONS:

General:

Patients should be advised to avoid activities with potential risks.

Head Injury and Increased Intracranial Pressure:

As with other opioids, the use of Butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, Butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control:

Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease:

In patients with hepatic or renal impairment, the initial dose of Butorphanol Tartrate injection should generally be half the recommended adult dose (0.5 mg IV and 1.0 mg

IM). Repeat doses in these patients should be determined by the patient's response rather than at fixed intervals but will generally be no less than 6 hours apart.

Cardiovascular Effects:

Because Butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of Butorphanol in patients with acute myocardial infarction, ventricular dysfunction or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during Butorphanol therapy. In such cases, Butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

4.4 Special warnings and special precautions for use: [contd]

WARNINGS:

Patients Dependent on Narcotics:

Because of its opioid antagonist properties, Butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning Butorphanol therapy. In patients taking opioid analgesics chronically, Butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of Butorphanol to such patients.

Drug Abuse and Dependence:

Drug Abuse-Butorphanol Tartrate, by all routes of administration, has been associated with episodes of abuse.

Physical Dependence, Tolerance, and Withdrawal-Prolonged, continuous use of Butorphanol Tartrate may result in physical dependence or tolerance (a decrease in response to a given dose). Abrupt cessation of use by patients with physical dependence may result in symptoms of withdrawal.

Note-Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence.

4.5 Interaction with other FPPs and other forms of interaction:

Concurrent use of Butorphanol with central nervous system depressants (eg, alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of Butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when

administered concomitantly with drugs that potentiate the action of opioids.It is not known if the effects of Butorphanol is altered by other concomitant medications that affect hepatic metabolism of drugs (erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.No information is available about the use of Butorphanol concurrently with MAO inhibitors.

4.6 Pregnancy and lactation:

Pregnancy Category C:

Reproduction studies in mice, rats, and rabbits during organogenesis did not reveal any teratogenic potential to Butorphanol.There are no adequate and well-controlled studies of Butorphanol Tartrate in pregnant women before 37 weeks of gestation.

Butorphanol Tartrate should be used during pregnancy only if the potential benefit justifies the potential risk to the infant.

Labor and Delivery:

There have been rare reports of infant respiratory distress/apnea following the administration of Butorphanol Tartrate injection during labor. The reports of respiratory distress/apnea have been associated with administration of a dose within 2 hours of delivery, use of multiple doses, use with additional analgesic or sedative drugs or use in preterm pregnancies.

Nursing Mothers:

Butorphanol has been detected in milk following administration of Butorphanol Tartrate injection to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 µg/L of milk in a mother receiving 2 mg IM four times a day).

4.7 Effects on Ability to drive & Use Machines:

It is not advisable to drive & use machines after Butorphanol has been adminsitered as common side effects are drowsiness & dizziness.

4.8 ADVERSE REACTIONS:

The most frequently reported adverse experiences across all clinical trials with Butorphanol Tartrate injection were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%).

The following adverse experiences were reported at a frequency of 1% or greater in clinical trials and were considered to be probably related to the use of Butorphanol.

Body as a Whole: asthenia/lethargy, headache, sensation of heat.

Cardiovascular: vasodilation, palpitations.

4.8 ADVERSE REACTIONS: [contd]

Digestive: anorexia, constipation, dry mouth, nausea and/or vomiting, stomach pain.

Nervous: anxiety, confusion, dizziness, euphoria, floating feeling, insomnia, nervousness, paresthesia, somnolence, tremor.

Respiratory: bronchitis, cough, dyspnea, epistaxis, nasal congestion, nasal irritation, pharyngitis, rhinitis, sinus congestion, sinusitis, upper respiratory tract infection.

Skin and Appendages: sweating/clammy, pruritus.

Special Senses: blurred vision, ear pain, tinnitus, unpleasant taste.

The following adverse experiences were reported with a frequency of less than 1% in clinical trials and were considered to be probably related to the use of Butorphanol.

Cardiovascular: hypotension, syncope.

Nervous: abnormal dreams, agitation, dysphoria, hostility, hallucinations, withdrawal symptoms.

Skin and Appendages: rash/hives.

Urogenital: impaired urination.

4.9 OVERDOSAGE AND TREATMENT OF OVERDOSAGE:

Clinical Manifestations:

The clinical manifestations of Butorphanol overdose are those of opioid drugs in general. Consequences of overdose vary with the amount of Butorphanol ingested and individual response to the effects of opiates. The most serious symptoms are hypoventilation, cardiovascular insufficiency, coma, and death. Butorphanol overdose may be associated with ingestion of multiple drugs.

Overdose can occur due to accidental or intentional misuse of Butorphanol, especially in young children who may gain access to the drug at home.

Treatment:

The management of suspected Butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of

the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness, and vital signs.

4.9 OVERDOSAGE AND TREATMENT OF OVERDOSAGE: [contd]

Clinical Manifestations: [contd]

Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required.

An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of Butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

In managing cases of suspected Butorphanol overdosage, the possibility of multiple drug ingestion should always be considered.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacotherapeutic group: Opioid mixed agonist-antagonists Analgesic agent.

ATC code: N02AF01

Mechanism of action:

General Pharmacology and Mechanism of Action:

Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). It is also an agonist at *k*-opioid receptors. Its interactions with these receptors in the central nervous system apparently mediate most of its pharmacologic effects, including analgesia.

In addition to analgesia, CNS effects include depression of spontaneous respiratory activity and cough, stimulation of the emetic center, miosis, and sedation. Effects possibly mediated by non-CNS mechanisms include alteration in cardiovascular resistance and capacitance, bronchomotor tone, gastrointestinal secretory and motor activity, and bladder sphincter activity.

The pharmacological activity of Butorphanol metabolites has not been studied in humans; in animal studies, Butorphanol metabolites have demonstrated some analgesic activity.

Butorphanol, like other mixed agonist-antagonists with a high affinity for the *k*-receptor, may produce unpleasant psychotomimetic effects in some individuals.

5. PHARMACOLOGICAL PROPERTIES: [contd]

Mechanism of action: **[contd]**

Nausea and/or vomiting may be produced by doses of 1 mg or more administered by any route.

Butorphanol Tartrate demonstrates antitussive effects in animals at doses less than those required for analgesia.

Pharmacodynamics:

The analgesic effect of Butorphanol is influenced by the route of administration. Onset of analgesia is within a few minutes for intravenous administration and within 15 minutes for intramuscular injection. Peak analgesic activity occurs within 30-60 minutes following intravenous and intramuscular administration.

The duration of analgesia varies depending on the pain model as well as the route of administration, but is generally 3-4 hours with IM and IV doses as defined by the time 50% of patients required remedication. In postoperative studies, the duration of analgesia with IV or IM Butorphanol was similar to morphine, meperidine and pentazocine when administered in the same fashion at equipotent doses.

5.2 Pharmacokinetic properties:

Absorption: Butorphanol Tartrate is rapidly absorbed after IM injection and peak plasma levels are reached in 20-40 minutes. Following its initial absorption/distribution phase, the single dose pharmacokinetics of Butorphanol by the intravenous and intramuscular route is similar. Serum protein binding is independent of concentration over the range achieved in clinical practice (up to 7 ng/mL) with a bound fraction of approximately 80%.

Distribution: The volume of distribution of Butorphanol varies from 305-901 liters and total body clearance from 52-154 liters/hour. The drug is transported across the blood brain and placental barriers and into human milk.

Metabolism: Butorphanol is extensively metabolized in the liver. Metabolism is qualitatively and quantitatively similar following intravenous or intramuscular administration.

The major metabolite of Butorphanol is hydroxyl butorphanol, while norbutorphanol is produced in small amounts.

5. PHARMACOLOGICAL PROPERTIES: [contd]

5.2 Pharmacokinetic properties: [contd]

Metabolism:

Both have been detected in plasma following administration of Butorphanol, with nor butorphanol present at trace levels at most time points.

Elimination: Elimination occurs by urine and fecal excretion. When 3H labelled Butorphanol is administered to normal subjects, most (70-80%) of the dose is recovered in the urine, while approximately 15% is recovered in the feces. About 5% of the dose is recovered in the urine as Butorphanol. Forty-nine percent is eliminated in the urine as hydroxylbutorphanol. Less than 5% is excreted in the urine as norbutorphanol.

Pharmacokinetics in Elderly Patients:

Butorphanol pharmacokinetics in the elderly differ from younger patients . Elimination half-life is increased in the elderly (6.6 hours as opposed to 4.7 hours in younger subjects).

Pharmacokinetics in Renally Impaired Patients :

In renally impaired patients with creatinine clearances < 30 mL/min, the elimination half-life was approximately doubled and the total body clearance was approximately one half (10.5 hours [clearance 150 L/h] compared to 5.8 hours [clearance 260 L/h] in healthy subjects). No effect on Cmax or Tmax was observed after a single dose.

Pharmacokinetics in Hepatic Impaired Patients :

After intravenous administration to patients with hepatic impairment, the elimination half-life of Butorphanol was approximately tripled and total body clearance was approximately one half (half-life 16.8 hours, clearance 92 L/h) compared to healthy subjects (half-life 4.8 hours, clearance 175 L/h). The exposure of hepatically impaired patients to Butorphanol was significantly greater (about 2-fold) than that in healthy subjects.

5.3 Preclinical safety data:

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Preclinical studies on analgesic effects:

In preclinical laboratory animal studies, Butorphanol produces antinociception in a variety of models in rhesus monkeys . In higher demand thermal antinociception assays, however, butorphanol fails to produce antinociception and will block the effects of higher efficacy μ agonists such as etonitazene, morphine.Interestingly,

Butorphanol and morphine blocked U50,488 antinociception in these high temperature thermal assays. Similarly, in the squirrel monkey shock-titration model of analgesia, Butorphanol produced modest increases in median shock levels (i.e., titrated the shock to a higher level) than methadone and U50,488 yet also dose-dependently antagonized the antinociception produced by methadone and U50,488 . These studies support the notion that Butorphanol is a lower efficacy agonist at μ and κ opioid receptors than morphine, methadone and U50,488, respectively, but the expression of the κ agonist effects may depend on species examined. In preclinical research studies using non-drug-abusing human volunteers, experimental pain induced by cold stressors modulated the subjective effects of Butorphanol, i.v., in females but not males B. However, in rhesus monkeys, Butorphanol produced greater - 4 - 4 34th ECDD 2006/4.1 Butorphanol antinociceptive effects in males than ovariectomized females although no difference was observed after treatment with estradiol.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Sodium Citrate(Injection grade), Sodium Chloride, Citric Acid monohydrate & Water for injection.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life: 30 MONTHS.

6.4 Special precautions for storage:

Store at a temperature not exceeding 30 °C.
KEEP OUT OF REACH OF CHILDREN.
PROTECT FROM MOISTURE AND LIGHT.

6.5 Nature and contents of container:

1 ml ampoule having yellow coloured ring and yellow dot printed on it.5 such duly labeled ampoules are packed in a blister tray .Such 1 tray of 5 ampoules is further packed in a printed carton along with pack insert.

6.6 Instructions for use and handling:

No special requirements. Any unused product or waste material should be disposed off in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER:

ARISTO PHARMACEUTICALS PRIVATE LIMITED

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8. MA number issued by Ethiopian FDA:

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9. Date of first authorization/renewal of the authorization:

13-05-2022

10. DATE OF REVISION OF THE TEXT:

05-07-2023