1. NAME OF THE MEDICINAL PRODUCT:
Temgesic® 0.2 mg Sublingual Tablet
Brand of buprenorphine hydrochloride

Indivior

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Buprenorphine hydrochloride 216 μg/tablet, equivalent to 200 μg buprenorphine base.

3. PHARMACEUTICAL FORM:
Temgesic 0.2mg Sublingual Tablets are white to creamy white, circular, biconvex tablets engraved on one side with the letter L. Each Temgesic Sublingual Tablet contains 0.216 mg buprenorphine hydrochloride, equivalent to 0.2 mg buprenorphine base.

The sublingual formulation is not designed to be split or broken.

4. CLINICAL PARTICULARS:
4.1 Therapeutic indications:
As a potent analgesic for use in moderate to severe pain.

4.2 Posology and method of administration:
The tablet should not be chewed or swallowed as this will reduce efficacy.

Adults and children over 12 years old:
1 to 2 tablets (200 to 400 micrograms) to be dissolved under the tongue (sublingually) every 6-8 hours or as required. The recommended starting dose for moderate to severe pain of the type typically presenting in general practice is one to two tablets (200 to 400 micrograms) every 8 hours. There is no indication that dosage needs to be modified for the elderly.

Temgesic Sublingual Tablets may be employed in balanced anaesthetic techniques as a premedication at a dose of 400 micrograms.

Elderly:
There is no indication that dosage needs to be modified for the elderly.

Children under 12 years:
Temgesic Sublingual Tablets are suitable for use in children as follows:
18-26 kg (35-55 lb): 100 micrograms (half a tablet)
25-37 kg (65-82.5 lb): 100-200 micrograms (half to one tablet)
37.5-50 kg (82.5-110 lb): 200-300 micrograms (one to one and a half tablets)
There is no clinical experience in infants below the age of six months.

Sublingual administration is not suitable for children under the age of six years.

4.3 Contraindications:
Patients with impaired respiratory functions. Patients with severe hepatic impairment. Patients with concurrently given MAO inhibitors. Patients who are pregnant. Not to be given to patients who are known to be allergic to Temgesic or other opiates. Hypersensitivity to any of the constituents.

4.4 Special warnings and precautions for use:

Dependence

Controlled human and animal studies indicate that buprenorphine has a substantially lower dependence liability than pure agonist analgesics. Following chronic use, abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

In patients abusing opioids in moderate doses, substitution with buprenorphine may prevent withdrawal symptoms. In man limited euphorigenic effects have been observed. This has resulted in some abuse of the product and cautions should be exercised when prescribing it to patients known to have or suspected of having problems with drug abuse.

There is evidence to indicate that therapeutic doses of buprenorphine do not reduce the analgesic efficacy of standard doses of an opioid agonist, and that when buprenorphine is employed within the normal range, standard doses of opioid agents may be administered before the effects of the former have ended without compromising analgesia. However, in individuals on high doses of opioids, buprenorphine may precipitate abstinence effects due to its properties as a partial agonist.

Use in ambulatory patients

Temgesic may cause drowsiness which may be potentiated by other centrally-acting agents, including alcohol, tranquilisers, sedatives and hypnotics. Ambulant patients should be warned not to drive or operating machinery until they are certain they can tolerate Temgesic.

Respiratory depression

Temgesic occasionally causes significant respiratory depression and, as with other strong centrally-acting agents, care should be taken when treating patients with impaired respiratory function or patients who are receiving drugs with can cause CNS or respiratory depression. Although volunteer studies have indicated that opiate antagonists may not fully reverse the effects of Temgesic, clinical experience has shown that naloxone may be of benefit in reversing reduced respiratory rate. Respiratory stimulants such as Doxepram are also effective. The intensity and duration of action may be affected in patients with impaired liver function.

Hepatic impairment

The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a postmarketing study. Since buprenorphine is extensively metabolized, plasma levels were found to be elevated for buprenorphine in patients with hepatic impairment. Buprenorphine may be used in patients with mild and moderate hepatic impairment with dosage adjustment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Buprenorphine should not be used in severe hepatic impairment.

Temgesic has been shown to increase intracholedochal pressure to a similar degree as other opioid analgesics, and thus should be administered with caution to patients with dysfunction of the biliary tract.

Renal disease

Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine; therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min).

Interaction with other central nervous system depressants
Patients receiving Temgesic in the presence of other opioid analgesics, general anaesthetics, antihistamines, benzodiazepines, phenothiazines, other tranquilisers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, it is particularly important that the dose of one or both agents be reduced.

Head injury and increased intracranial pressure
Temgesic, like other potent opioids, may itself elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased.

Temgesic can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Cardiovascular effects
Temgesic may cause a slight reduction in pulse rate and blood pressure in some patients.
Like other opioids, Temgesic may produce orthostatic hypotension in ambulatory patients.

Acute abdominal conditions
As with other mu-opioid receptor agonists, the administration of buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Other opioid class warnings
Temgesic should be administered with caution in patients with the following conditions:

- elderly or debilitated
- myxoedema or hypothyroidism
- adrenal cortical insufficiency (e.g., Addison's disease)
- toxic psychoses
- prostatic hypertrophy or urethral stricture
- acute alcoholism
- delirium tremens
- kyophoscoliosis

4.5 Interaction with other medicinal products and other forms of interaction:
Alcohol
Temgesic should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine

Benzodiazepines
A number of deaths and cases of coma have occurred when addicts have intravenously misused Temgesic and benzodiazepines concomitantly.

There have been reports of respiratory and cardiovascular collapse in patients who received therapeutic doses of diazepam and analgesic doses of Temgesic; therefore, dosages must be limited and this combination must especially be avoided in cases where there is a risk of misuse. Patients must use

benzodiazepines concurrently with this product only as prescribed (see section 4.4).Other central nervous system depressants
Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. The reduced level of alertness can make driving and using machines hazardous.

CYP3A4 inhibitors
Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of buprenorphine. Thus patients receiving buprenorphine co-administered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), or protease inhibitors (e.g., ritanovir) should be carefully monitored.
Caution is advised when administering Temgesic to patients receiving these medications, and if necessary, dose adjustments should be considered.

CYP3A4 inducers
Cytochrome P450 inducers, such as phenobarbital, rifampin, carbamazepine, and phenytoin, induce metabolism and may cause increased clearance of buprenorphine. Caution is advised when administering Temgesic to patients receiving these medications, and if necessary, dose adjustments should be considered.

Naltrexone and other opioid antagonists
Opioid antagonists such as naltrexone may antagonize the pharmacologic effect of buprenorphine. Patients treated with opioid antagonists such as naltrexone may not receive the intended analgesic effects of Temgesic.

Patients who have developed physical dependence to the effects of buprenorphine may experience a sudden onset of opioid withdrawal effects.

Other opioid analgesics
The analgesic effects of full agonist opioids may be competitively diminished by the partial agonist buprenorphine.

For patients who have developed a physiological dependence to full opioid agonists, administration of the partial agonist buprenorphine may elicit withdrawal symptoms.

Other
Halothane is known to decrease hepatic clearance. Since hepatic elimination plays a relatively large role (~70%) in the overall clearance of buprenorphine, lower initial doses and cautious titration of dosage may be required when used with halothane.

4.6 Interference with laboratory tests:
Temgesic has no known effects on diagnostic laboratory tests.

4.7 Pregnancy and lactation:
Temgesic is not intended for use during pregnancy. Animal studies indicate that the amounts of buprenorphine excreted in milk are very low and in human use are unlikely to be of clinical significance to the baby. There is indirect evidence in animal studies to suggest that Temgesic may cause a reduction

in milk flow during lactation. Although this occurred only at doses well in excess of the human dose, it should be borne in mind when treating lactating women.

4.8 Undesirable effects:

4.8.1 Clinical Trial Data

Summary of the safety profile: Very commonly reported adverse reactions reported in clinical studies were sedation, vertigo, dizziness, and nausea.

Tabulated list of adverse reactions: Table 1 lists adverse drug reactions reported in clinical studies. The frequency of possible side effects listed below is defined using the following convention: 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).

Table 1: Treatment-related adverse reactions reported in clinical studies of buprenorphine [Temgesic]

Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Immune system disorders			
			Hypersensitivity
Metabolism and nutrition disorders			
			Decreased appetite
Psychiatric disorders			
		Confusional state Euphoric mood Nervousness Depression Psychotic disorder Hallucination Depersonalisation	Dysphoria Agitation
Nervous system disorders			
Sedation Dizziness	Headache	Dysarthria Paraesthesia Coma Tremor	Convulsion Coordination abnormal
Eye disorders			
	Miosis	Vision blurred Diplopia Visual impairment Conjunctivitis	
Ear and labyrinth disorders			
Vertigo		Tinnitus	
Cardiac disorders			
		Tachycardia Bradycardia Cyanosis Atrioventricular block second degree	
Vascular disorders			
	Hypotension	Hypertension Pallor	
Respiratory, thoracic and mediastinal disorders			
	Hypoventilation	Dyspnoea Apnoea	
Gastrointestinal disorders			
Nausea	Vomiting	Dry mouth Constipation Dyspepsia Flatulence	Diarrhoea
Skin and subcutaneous tissue disorders			
	Hyperhidrosis	Pruritus Rash	Urticaria
Renal and urinary disorders			
		Urinary retention	

General disorders and administration site conditions			
		Asthenia Fatigue Malaise	

4.8.2 Post-marketing Data

Tabulated list of adverse reactions: The following is a list of the most commonly reported adverse drug reactions reported during post-marketing surveillance. Events occurring in at least 1% of reports by healthcare professionals and considered expected, are included. Serious reactions of anaphylactic shock, bronchospasm, and angioneurotic oedema have occurred at unknown rates, and are also included in Table 2. These adverse drug reactions are presented by MedDRA System, Organ, Class in internationally agreed order by preferred term and frequency of reporting.

Table 2: Spontaneous Adverse Drug Reactions Reported by Body System

MedDRA System Organ Class	**Preferred Term**
Immune system disorders	Anaphylactic shock*
Psychiatric disorders	Confusional state Drug dependence Hallucination
Nervous system disorders	Somnolence Dizziness Headache
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Respiratory depression Bronchospasm*
Gastrointestinal disorders	Nausea Vomiting
Skin and subcutaneous tissue disorders	Pruritus Rash Hyperhidrosis Angioedema*
General disorders and administration site conditions	Drug ineffective Drug interaction Fatigue

*frequency of reporting is less than 1% of post-marketing reports, but these items are included in Table 2 based upon seriousness of occurrence.

4.9 Overdose:

Temgesic Sublingual has a wide safety margin and in clinical practice doses of buprenorphine well in excess of these recommended have been used without untoward effect. Over-dosage by the sublingual route is unlikely.

Symptoms

Manifestations of acute overdose include miosis, sedation, hypotension, respiratory depression and death. Nausea and vomiting may be observed. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death.

Treatment

In the event of overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be performed. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available.

If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Use of an opioid antagonist (i.e., naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents. If naloxone is used, the long duration of action of buprenorphine should be taken into

consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose.
Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. If infusion is not possible, repeated dosing with naloxone may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Buprenorphine is a μ (mu) opioid partial agonist and k (kappa) antagonist. It is a strong analgesic of the partial agonist (mixed agonist (antagonist) class.

5.2 Pharmacokinetic properties:

Absorption

When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjungation in the small intestine. The use of this medication by oral route is therefore inappropriate.
Peak plasma concentrations are achieved 90 minutes after sublingual administration.

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase and a half - life of 2 to 5 hours.

Metabolism and elimination

Buprenorphine is oxidatively metabolised by 14-N-dealkylation to N-desalkyl-buprenorphine (also known as norbuprenorphine) via cytochrome P450 CYP3A4 and by glucuroconjungation of the parent molecule and the dealkylated metabolite. Norbuprenorphine is μ (mu) agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri- exponential, with long terminal elimination phase4 of 20-25 hours, due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (80%), the rest being eliminated in the urine.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Lactose,
Mannitol
Maize starch
Povidone
Citric acid
Magnesium stearate
Sodium citrate
Purified water
Alcohol (96%)

6.2 Shelf life:

36 months

6.3 Special precautions for storage:
Cool, dry place below 30°C, protect from direct sunlight.

6.4 Nature and contents of container:
Temgesic Sublingual Tablets: Box of 50.

Keep out of reach of children.
Further information can be obtained from the doctor or pharmacist.

Manufactured by Reckitt Benckiser Healthcare (UK) Ltd., Dansom Lane, Hull, HU8 7DS
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