Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine 2.5 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2.5 mg of Bupivacaine hydrochloride monohydrate
Each vial with 10 ml solution contains 25 mg of bupivacaine hydrochloride monohydrate.

Each vial with 20 ml solution contains 50 mg of bupivacaine hydrochloride monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

A clear, colourless, aqueous, sterile solution.

pH of the solution is between 4.0 and 6.5 and osmolarity is 290 mOsmol/Litre.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Surgical anaesthesia in adults and adolescents
- Acute pain management in adults, infants and children above 1 year of age

4.2 Posology and method of administration

The dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and the technique of anaesthesia used. The lowest dosage needed to provide effective anaesthesia should be administered. For most indications, the duration of anaesthesia with Bupivacaine solutions is such that a single dose is sufficient.

The maximum dosage must be determined by evaluating the size and physical status of the patient and considering the usual rate of systemic absorption from a particular injection site. Experience to date indicates a single dose of up to 150mg bupivacaine hydrochloride monohydrate. Doses of up to 50mg 2-hourly may subsequently be used. A maximum dose of 2mg/kg should not be exceeded in any four-hour period.

When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the risks of reaching a toxic plasma concentration must be considered.

The dosages in the following table are recommended as a guide for use in the average adult. Individual variations in onset and duration occur. For young, elderly or debilitated patients, these doses should be reduced.

Dosage recommendations for adults

	Conc mg/ml	**Volume ml**	**Dosemg**	**Onsetmin**	**Duration of effect hours**
SurgicalAnaesthesia					
LumbarEpiduralAdministration1					
Surgery	5	15-30	75-150	15-30	2-3
Caesarean Section	5	15-30	75-150	15-30	2-3
ThoracicEpiduralAdministration1					

Surgery	2.5	5-15	12.5-37.5	10-15	1.5-2
	5	5-10	25-50	10-15	2-3
CaudalEpiduralBlock1					
	2.5	20-30	50-75	20-30	1-2
	5	20-30	100-150	15-30	2-3
MajorNerveBlock2 (e.g. brachial plexus, femoral, sciatic)	5	10-35	50-175	15-30	4-8
Fieldblock (e.g. minor nerve blocks and infiltration)	2.5	<60	<150	1-3	3-4
	5	≤30	≤ 150	1-10	3-8

AcutePainManagement					
LumbarEpiduralAdministration					
Intermittent injections3 (e.g. post-operative pain relief)	2.5	6-15 (Minimum interval 30 minutes)	15-37.5 (Minimum interval 30 minutes)	2-5	1-2
Continuous infusion	2.5	5-7.5/h	12.5-18.8/ h	-	-
ThoracicEpiduralAdministration					
Continuous infusion	2.5	4-7.5/h	10-18.8/h	-	-
Intra-ArticularBlock6 (e.g. single injection following knee arthroscopy)	2.5	≤40	≤100	5-10	2-4 h after wash out
FieldBlock (e.g. minor nerve blocks and infiltration)	2.5	≤60	≤150	1-3	3-4

1) Dose includes test dose.
2) The dose for a major nerve block must be adjusted according to site of administration and patient status.
Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used, see also section 4.4.
3) In total ≤500 mg/24 h.
4) This solution is often used for epidural administration in combination with a suitable opioid for pain management. In total ≤500 mg/24 h.
5) If additional bupivacaine is used by any other techniques in the same patient, an overall dose limit of 150 mg should not be exceeded.
6) There have been post-marketing reports of chrondolysin in patients receiving post-operative intra-articular continuous infusion of local anesthetics. Bupivacaine is not approved for continuous intra-articular infusion (See also section 4.4).

In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When a less intense block is required, the use of a lower concentration is indicated. The volume of medicinal product used will affect the extent of spread of anaesthesia.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25-50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a preceding test dose of 3-5 ml bupivacaine containing adrenaline (epinephrine) is recommended.

An inadvertent intravascular injection may be recognised by a temporary increase in
heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

Paediatric population 1to12 years of age

Paediatric regional anaesthetic procedures should be performed by qualified clinicians who are familiar with this population and the technique.

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements. The lowest dose required for adequate analgesia should be used.

Dosagerecommendationsforchildren 1 to 12 years of age

	Conc. mg/ml	Volume ml/kg	Dose mg/kg	Onsetmin	Duration ofeffects hours
AcutePainManagement(pre- and Postoperative)					
CaudalEpidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
LumbarEpidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
ThoracicEpidural Administrationb)	2.5	0.6-0.8	1.5-2	20-30	2-6
FieldBlock (eg, minor nerve blocks and infiltration)	2.5 5.0		0.5-2.0 0.5-2.0		
Peripheral Nerve Blocks (e.g ilioinguinal –iliohypogastric)	2.5 5.0		0.5-2.0[a] 0.5-2.0[a]		

a) The onset and duration of peripheral nerve blocks depend on the type of block and the dose administered.
b) Thoracic epidural blocks need to be given by incremental dosage until the desired level of anaesthesia is achieved.

In children the dosage should be calculated on a weight basis up to 2 mg/kg.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose. This should be injected slowly in incremental doses, particularly in the lumbar and thoracic epidural routes, constantly and closely
observing the patient's vital functions.

Peritonsillar infiltration has been performed in children above 2 years of age with bupivacaine 2.5 mg/ml at a dose of 7.5-12.5mg per tonsil.

Ilioinguinal-iliohypogastric blocks have been performed in children aged 1 year or older with bupivacaine 2.5 mg/ml at a dose of 0.1-0.5 ml/kg equivalent to 0.25-1.25 mg/kg. Children aged 5 years or older have received bupivacaine 5 mg/ml at a dose of 1.25-2 mg/kg.

For penile blocks bupivacaine 5 mg/ml has been used at total doses of 0.2-0.5 ml/kg equivalent to 1-2.5 mg/kg.

ThesafetyandefficacyofBupivacaineinchildren< 1 yearofagehavenot been established.Onlylimiteddataareavailable.

Safetyandefficacyofintermittentepiduralbolusinjectionorcontinuousinfusionhave not beenestablished.Onlylimiteddataisavailable.

Method of administration
The medicinal product is for epidural use, intraarticular use, subcutaneous use or perineural use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Bupivacaine hydrochloride solutions are contraindicated in patients with hypersensitivity to local anaesthetic agents of the amide type.

Solutions of bupivacaine hydrochloride are contraindicated for injection into inflamed or infected areas and for intravenous regional anaesthesia (Bier's-block).and obstetrical paracervical block

4.4 Special warnings and precautions for use

Generalprecautionsandriskofbupivacianeuse:
There have been reports of cardiac arrest or death during use of bupivacaine for epidural anaesthesia or peripheral nerve blockade In some instances, resuscitation has been difficult or impossible despite apparently adequate preparation and management.

Like all local anaesthetic drugs, bupivacaine may cause acute toxicity effects on the central nervous and cardiovascular systems, if utilised for local anaesthetic procedures resulting in high blood concentrations of the drug. This is especially the case after unintentional intravascular administration or injection into highly vascular areas. Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine.

Adequate resuscitation equipment should be available whenever local or general anaesthesia is administered. Overdosage or accidental intravenous injection may give rise to toxic reactions with marked restlessness, twitching or convulsions followed by coma with apnoea and cardiovascular collapse.
Regional or local anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and drugs necessary for monitoring and emergency resuscitation should be immediately available. Patients receiving major blocks should be in an optimal condition and have an i.v. line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid intravascular injection (see section 4.2) and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications (see section 4.9).

Major peripheral nerve blocks may require the administration of a large volume of local anaesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or systemic absorption. This may lead to high plasma concentrations.

Although regional anaesthesia is frequently the optimal anaesthetic technique, some patients require special attention in order to reduce the risk of dangerous side effects:

- Older people and patients in poor general condition.
- Patients with partial or complete heart block – due to the fact that local anaesthetics may depress myocardial conduction.
- Patients with advanced liver disease or severe renal dysfunction.
- Patients in late stages of pregnancy.
- Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be kept under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of the local anaesthetic drug used:

- Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Epidural anaesthesia should be used with caution in patients with impaired cardiovascular function.
- Retrobulbar injections may very occasionally reach the cranial subarachnoid space causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc. These must be diagnosed and treated promptly.
- Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves. The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors may aggravate tissue reactions and should be used only when indicated.
- Injections in the head and neck regions may be made inadvertently into an artery, which may cause immediate cerebral symptoms even at low doses.
- Paracervical block can sometimes cause foetal bradycardia/tachycardia, and careful monitoring of the foetal heart rate is necessary.

- There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for Bupivacaine

Hypotension and bradycardia may occur as normal physiological phenomena following sympathetic block with central neural blocks. Epidural anaesthesia and subarachnoid block may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g. by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

The lowest dose that produces effective anaesthesia should be used. Injection of repeated doses of bupivacaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug. Tolerance varies with the status of the patient. Debilitated, elderly or acutely ill patients should be given reduced doses commensurate with their physical status. The maximum recommended dose should not be exceeded.

The continuous or repeated administration of this product may give rise to cumulative toxicity and tachyphylaxis. Bupivacaine hydrochloride should be used with caution in patients with epilepsy, impaired cardiac conduction or in those with hepatic or renal damage.

Bupivacaine solutions should be used with caution in persons with known drug sensitivities. Patients allergic to ester-type local anaesthetic drugs (procaine, tetracaine, benzocaine, etc.) have not shown cross-sensitivity to agents of the amide type such as bupivacaine.

Since bupivacaine is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow (e.g. in severe shock).

Hepatic dysfunction, with reversible increases of alanine aminotransferase (ALT), alkaline phosphates (AlkP) and bilirubin, has been observed following repeated injections or long-term infusions of bupivacaine. Association between bupivacaine use and the development of drug-induced liver injury (DILI) has been reported in a small number of literature reports especially with prolonged use. While the pathophysiology of this reaction remains unclear, immediate withdrawal of bupivacaine has shown rapid clinical improvement. If signs of hepatic dysfunction are observed during administration with bupivacaine, the medicinal product should be discontinued.

Children should be given doses commensurate with their age and weight.

When bupivacaine is administered as an intra-articular injection, caution is advised when recent major intra-articular trauma is suspected or extensive raw surfaces within the joint have been created by the surgical procedure, as that may accelerate absorption and result in higher plasma concentrations.

Paediatricpopulation:

The use of bupivacaine for intra-articular block in children 1 to 12 years of age has not been documented.

The use of bupivacaine for major nerve block in children 1 to 12 years of age has not been documented.

For epidural anaesthesia children should be given incremental doses commensurate with their age and weight as especially epidural anaesthesia at a thoracic level may result in severe hypotension and respiratory impairment.

The medicinal product contains sodium.
Each ml of the solution contains 3.15 mg (0.14 mmol) of Sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive.

Specific interaction studies with bupivacaine and anti-arrhythmic medicinal product class III (e.g. amiodarone) have not been performed, but caution should be advised, (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of bupivacaine in human pregnancy. Animal studies have shown decreased pup survival and embryotoxic effects (see section 5.3). The potential risk for human is unknown. Bupivacaine injection should therefore not be given in pregnancy unless the benefits are considered to outweigh the risks.

Use in obstetrics
Bupivacaine solutions are contraindicated for use in paracervical block in obstetrics, because foetal bradycardia may occur following paracervical block (see section 4.3).

Breast-feeding
Bupivacaine enters the mother's milk, but in such small quantities that there is no risk of affecting the child at therapeutic dose levels.

4.7 Effects on ability to drive and use machines

Bupivacaine has minor influence on the ability to drive and use machines.
Beside the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and co-ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

General
Bupivacaine causes systemic toxicity similar to that observed with other local anaesthetic agents. It is caused by high plasma concentrations as a result of excessive dosage, rapid absorption or, most commonly, inadvertent intravascular injection.. Such reactions involve the central nervous system and the cardiovascular system. CNS reactions are characterised by numbness of the tongue, light-headedness, dizziness, blurred vision and muscle twitch, followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest.

Cardiovascular reactions are depressant and are characterised by hypotension and myocardial depression. They may be the result of hypoxia due to convulsions and apnoea as well as a direct effect.

Adverse reactions caused by the drug per se are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia), events caused directly (e.g. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture. Neurological damage is a rare but well recognised consequence of regional, and particularly epidural and spinal anaesthesia.
The incidence of adverse neurologic reactions associated with the use of local anaesthetics is very low and have included persistent anaesthesia, paraesthesia, weakness, paralysis of the lower extremities and loss of sphincter control. In rare cases, local anaesthetic preparations have been associated with allergic reactions (in the most severe instances anaphylactic shock).

System Organ Class	Frequency Classification	Adverse Drug Reaction
Immune system disorders	Rare	Allergic reactions, anaphylactic reaction/shock (see section 4.4)
Nervous system disorders	Common	Paraesthesia, dizziness
	Uncommon	Signs and symptoms of CNS toxicity (convulsions, paraesthesia circumoral, numbness of the tongue, hyperacusis, visual disturbances, loss of consciousness, tremor, light headedness, tinnitus, dysarthria)

	Rare	Neuropathy, peripheral nerve injury, arachnoiditis, paresis and paraplegia
Eye disorders	Rare	Diplopia
Cardiac disorders	Common	Bradycardia (see section 4.4)
Vascular disorders	Very Common	Hypotension (see section 4.4)
	Common	Hypertension (see section 4.5)
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
Renal and urinary disorders	Common	Urinary retention

Reportingofsuspectedadversereactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA PharmacovigilanceWebsite: www.hpra.ie

4.9 Overdose

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15-60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

Acutesystemictoxicity
Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system. Such reactions are caused by high blood concentrations of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see section 4.4). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the medicinal product, both quantitatively and qualitatively. Signs of toxicity in the central nervous system generally precede cardiovascular toxic effects, unless the patient is receiving a general anaesthetic or is heavily sedated with medicinal products such as benzodiazepine or barbiturate.

Centralnervoussystemtoxicityis a graded response with symptoms and signs of escalating severity. The first symptoms are usually, circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic medicinal product from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicinal product have been injected.

Cardiovascularsystemtoxicitymay be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent.

Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred
without prodromal CNS effects.

Paediatric population
Adverse drug reactions in children are similar to those in adults, however in children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during sedation or general anaesthesia.

Treatmentofacutetoxicity
If signs of acute systemic toxicity appear, injection of the local anaesthetic should be immediately stopped.

Treatment of a patient with systemic toxicity consists of arresting convulsions and ensuring adequate ventilation with oxygen, if necessary by assisted or controlled ventilation (respiration). Convulsions should be treated promptly by intravenous injection of an anticonvulsant.

Prolonged convulsions may jeopardise the patient's ventilation and oxygenation. Early endotracheal intubation must be considered in such situations. . If so, injection of a muscle relaxant (e.g. succinylcholine) will facilitate ventilation, and oxygenation can be controlled. Early endotracheal intubation must be considered in such situations.

Once convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required. If hypotension is present, however, a vasopressor, preferably one with inotropic activity, e.g. ephedrine should be given intravenously.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anesthetics, local; Amides
ATC code: N01BB01.

Bupivacaine is a potent amide local anaesthetic with a prolonged duration of action.
It affects sensory nerves more than motor nerves and is ideal for producing analgesia without motor blockade.

5.2 Pharmacokinetic properties

In adults, the terminal half-life of bupivacaine is 3.5 hours. The maximum blood concentration varies with the site of injection and is highest after intercostal nerve blockade.
Total dose, rather than concentration, is an important determinant of peak blood levels.
Bupivacaine is biodegraded in the liver and only 6% is excreted unchanged in the urine.
Paediatric population
In children the pharmacokinetics is similar to that in adults.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, acute and subchronic toxicity, non-clinical data reveal no special hazard other than those already reported elsewhere in this document.

The mutagenic and carcinogenic potential of bupivacaine has not been determined.

Bupivacaine crosses the placenta. In reproduction toxicity studies, decreased survival of the offspring of rats and embryolethality was noted in rabbits at bupivacaine doses, which were five- or nine-fold the maximum recommended daily dose in humans.

A study in rhesus monkeys suggested altered postnatal behaviour following exposition to bupivacaine at birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
0.4% Sodium hydroxide (for pH adjustment)

0.85% hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Bupivacaine may precipitate if diluted with alkaline solutions and should not be diluted or co-administered with sodium bicarbonate injections. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

After first opening: To be used immediately.

After dilution: Chemical and physical in use stability has been demonstrated for 36 hours at 25 °C.

From a microbiological point of view the product should be used immediately.

6.4 Special precautions for storage

Store below 30 °C. Do not refrigerate or freeze.

6.5 Nature and contents of container

10 ml type I clear glass vial with bromobutyl rubber closure
20 ml type I clear glass vial with bromobutyl rubber closure

Packsizes:
5, 10 x 10 ml Solution for Injection
1, 5, 10 x 20 ml Solution for Injection

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.
The solution / dilution should be inspected visually prior to use. Only clear solutions practically free from particles should be used.

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

Bupivacaine is compatible when admixed with 0.9% w/v sodium chloride
solution for injection, Ringer Lactate Solution and Sufentanil Citrate 50µg/ml.

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/035/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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