

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Yantil 4 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 4 mg tapentadol (as hydrochloride)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution
Clear, colourless solution
pH 3.5 to 4.5

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Yantil 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

The dosing regimen should be individualised 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 oral solution 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.
Daily doses greater than 700 mg tapentadol on the first day of treatment and maintenance daily doses greater than 600 mg tapentadol have not been studied and are therefore not recommended.
As soon as stable dosing regimen is achieved and longer treatment is anticipated, the possibility of switching the patient to therapy with the prolonged-release tablets Yantil SR should be considered.
As with all symptomatic treatments, the continued use of tapentadol must be evaluated on an ongoing basis.

Single dose of tapentadol prescribed	Volume (ml) to be administered
25 mg	6.25 ml
50 mg	12.5 ml
75 mg	18.75 ml
100 mg	25 ml

Discontinuation of treatment
Withdrawal symptoms could occur after abrupt discontinuation of treatment with tapentadol (see section 4.8). When a patient no longer requires therapy with tapentadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Renal Impairment
In patients with mild or moderate renal impairment a dosage adjustment is not required (see section 5.2).

Yantil has not been studied in controlled efficacy trials in patients with severe renal impairment, therefore the use in this population is not recommended (see sections 4.4 and 5.2).

Hepatic Impairment

In patients with mild hepatic impairment a dosage adjustment is not required (see section 5.2).

Yantil should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 25 mg tapentadol as oral solution and not be administered more frequently than once every 8 hours. At initiation of therapy a daily dose greater than 150 mg tapentadol is not recommended. Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval (see sections 4.4 and 5.2).

Yantil has not been studied in patients with severe hepatic impairment and therefore, use in this population is not recommended (see sections 4.4 and 5.2).

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 (see sections 4.2 and 5.2).

Paediatric Patients

The safety and efficacy of Yantil in children and adolescents below 18 years of age has not yet been established. Therefore Yantil is not recommended for use in this population.

Method of administration

Yantil can be taken with or without food.

Yantil oral solution can be taken either undiluted or diluted in water or any non-alcoholic drink. There is an oral syringe with an attached adaptor in the pack which is recommended to be used to take the exact volume needed from the bottle corresponding to the prescribed single dose of tapentadol.

Yantil can be taken via enteral tubes, e.g. nasogastric or percutaneous endoscopic gastrostomy (PEG) tubes.

4.3 Contraindications

Yantil is contraindicated

- in patients with hypersensitivity to tapentadol or to any of the excipients (see section 6.1)
- 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 (see section 4.5)

4.4 Special warnings and precautions for use

Potential for Abuse and Addiction/ Dependence Syndrome

Yantil has a potential for abuse and addiction. This should be considered when prescribing or dispensing Yantil 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.

Respiratory Depression

At high doses or in mu-opioid receptor agonist sensitive patients, Yantil may produce dose-related respiratory depression. Therefore, Yantil should be administered with caution to patients with impaired respiratory functions.

Alternative non-mu-opioid receptor agonist analgesics should be considered and Yantil 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 (see section 4.9).

Head Injury and Increased Intracranial Pressure

Yantil 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. Yantil should be used with caution in patients with head injury and brain tumors.

Seizures

Yantil 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 Yantil should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

Renal Impairment

Yantil has not been studied in controlled efficacy trials in patients with severe renal impairment, therefore the use in this population is not recommended (see section 4.2 and 5.2).

Hepatic Impairment

Subjects with mild and moderate hepatic impairment showed a 2-fold and 4.5-fold increase in systemic exposure, respectively, compared with subjects with normal hepatic function. Yantil should be used with caution in patients with moderate hepatic impairment (see section 4.2 and 5.2), especially upon initiation of treatment.

Yantil has not been studied in patients with severe hepatic impairment and therefore, use in this population is not recommended (see sections 4.2 and 5.2).

Use in Pancreatic/Biliary Tract Disease

Active substances with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. Yantil should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Concomitant treatment with monoamine oxidase inhibitors (MAOI)

Treatment with Yantil 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 (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Treatment with Yantil 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 (see section 4.4)

Medicinal products like benzodiazepines, barbiturates and opioids (analgesics, antitussives or substitution treatments) may enhance the risk of respiratory depression if taken in combination with Yantil. CNS depressants (e.g. benzodiazepines, antipsychotics, H1-antihistamines, opioids, alcohol) can enhance the sedative effect of tapentadol and impair vigilance. Therefore, when a combined therapy of Yantil with a respiratory or CNS depressant is contemplated, the reduction of dose of one or both agents should be considered.

In isolated cases 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). Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

There is no clinical data on the concomitant use of Yantil with mixed mu-opioid agonist/antagonists (like pentazocine, nalbuphine) or partial mu-opioid agonists (like buprenorphine). As with pure mu-opioid agonists, the analgesic effect provided by the mu-opioid component of Yantil may be theoretically reduced in such circumstances. Therefore, care

should be taken when combining Yantil with these medicinal products.

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 may lead to increased systemic exposure of tapentadol. Interaction studies with active substances that potentially could affect the glucuronidation (paracetamol, acetylsalicylic acid, naproxen and probenecid) did not result in any clinically relevant effect on the serum concentrations of tapentadol (see section 5.2). Interaction studies with substances that can affect absorption of tapentadol (omeprazole and metoclopramide) did not result in any clinically relevant effect on the serum concentrations of tapentadol (see section 5.2).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is very limited amount of data from the use in pregnant women.

Studies in animals have not shown teratogenic effects. However, delayed development and embryotoxicity were observed at doses resulting in exaggerated pharmacology. Effects on the postnatal development were already observed at the maternal NOAEL (see section 5.3).

Yantil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Labour and Delivery

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

Lactation

There is no information on the excretion of tapentadol in human milk. From a study in rat pups suckled by dams dosed with tapentadol it was concluded that tapentadol is excreted via milk (see section 5.3). Therefore, a risk to the suckling child cannot be excluded. Yantil should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

Yantil may have major influence on the ability to drive and use machines due to the fact that it may adversely affect central nervous system functions (see section 4.8). This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilisers (see section 4.4). Patients should be cautioned as to whether driving or use of machines is permitted.

4.8 Undesirable effects

The adverse drug reactions that were experienced by patients in the placebo controlled trials performed with Yantil were predominantly of mild and moderate severity. The most frequent adverse drug reactions were in the gastrointestinal and central nervous system (nausea, vomiting, somnolence, dizziness and headache).

The table below lists adverse drug reactions that were identified from clinical trials performed with another immediate release formulation of tapentadol (Yantil film-coated tablets). They 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).

ADVERSE DRUG REACTIONS				
System Organ Class	Frequency			
	Very common	Common	Uncommon	Rare
Immune system disorders				Drug Hypersensitivity including angioedema
Metabolism and nutrition disorders		Decreased appetite		
Psychiatric disorders		Anxiety, Confusional state, Hallucination, Sleep disorder, Abnormal dreams	Depressed mood, Disorientation, Agitation, Nervousness, Restlessness, Euphoric mood	Thinking abnormal
Nervous system disorders	Dizziness, Somnolence, Headache	Tremor	Disturbance in attention, Memory impairment, Presyncope, Sedation, Ataxia, Dysarthria, Hypoaesthesia, Paraesthesia, Muscle contractions involuntary	Convulsion, Depressed level of consciousness, Coordination abnormal
Eye disorders			Visual disturbance	
Cardiac disorders			Heart rate increased	Heart rate decreased
Vascular disorders		Flushing	Blood pressure decreased	
Respiratory, thoracic and mediastinal disorders			Respiratory depression, Oxygen saturation decreased, Dyspnoea	
Gastrointestinal disorders	Nausea, Vomiting	Constipation, Diarrhoea, Dyspepsia, Dry mouth	Abdominal discomfort	Impaired gastric emptying
Skin and subcutaneous tissue disorders		Pruritus, Hyperhidrosis, Rash	Urticaria	
Musculoskeletal and connective tissue disorder		Muscle spasms	Sensation of heaviness	
Renal and			Urinary hesitation,	

urinary disorders			Pollakiuria	
General disorders and administration site conditions		Asthenia, Fatigue, Feeling of body temperature change	Drug withdrawal syndrome, Oedema, Feeling abnormal, Feeling drunk, Irritability, Feeling of relaxation	

Clinical trials performed using another immediate release formulation of tapentadol (Yantil film-coated tablets) with patient exposure up to 90 days have shown little evidence of withdrawal symptoms upon abrupt discontinuations and these were generally classified as mild, when they occurred. Nevertheless, physicians should be vigilant for symptoms of withdrawal (see section 4.2) and treat patients accordingly should they occur.

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. For tapentadol data from clinical trials and post-marketing reports do not provide evidence for an increased risk.

4.9 Overdose

Human Experience

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.

Management of 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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 exerts its analgesic effects directly without a pharmacologically active metabolite.

Tapentadol demonstrated efficacy in preclinical models of nociceptive, neuropathic, visceral and inflammatory pain; Efficacy has been verified in clinical trials with another immediate-release formulation of tapentadol (film-coated tablets) covering nociceptive pain conditions including postoperative orthopaedic and abdominal pain as well as chronic pain due to osteoarthritis of the hip or knee. In general the analgesic effect of tapentadol in nociceptive pain

trials was similar to that observed with a strong opioid used as comparator.

Effects on the cardiovascular system: In a thorough human QT trial, no effect of multiple therapeutic and supratherapeutic doses of tapentadol on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Yantil in one or more subsets of the paediatric population in moderate to severe acute pain. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The bioavailability as assessed by $C_{\max}$ and AUC and all other pharmacokinetic parameters determined for tapentadol after administration of 100 mg tapentadol as oral solution were similar compared to a 100 mg film-coated tablet (another oral immediate-release formulation). Therefore the information given below based on trials with film-coated tablets is also applicable to the oral solution.

Absorption

Tapentadol is rapidly and completely absorbed after oral administration of PALEXIA. 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.

A multiple (every 6 hour) dose trial with doses ranging from 75 to 175 mg tapentadol 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 and its metabolite.

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. Based on efficacy data obtained at early assessment time points during phase II/III trials, the food effect does not appear to be of clinical relevance PALEXIA may be given with or without food.

Distribution

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

Metabolism and Elimination

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 phase 2 conjugation.

None of the metabolites contributes to the analgesic activity.

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

Special populations

Elderly

The mean exposure (AUC) to tapentadol was similar in a trial with elderly subjects (65-78 years of age) compared to young adults (19-43 years of age), with a 16% lower mean $C_{\max}$ observed in the elderly subject group compared to young adult subjects.

Renal Impairment

AUC and $C_{\max}$ of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide are 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Hepatic Impairment

Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild and moderate hepatic impairment groups in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for $C_{\max}$; and 1.2 and 1.4, respectively, for $t_{1/2}$. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Pharmacokinetic Interactions

Tapentadol is mainly metabolised by phase 2 glucuronidation, and only a small amount is metabolised by phase 1 oxidative pathways.

As glucuronidation is a high capacity/low affinity system, which is not easily saturated even in disease, and as therapeutic concentrations of active substances are generally well below the concentrations needed for potential inhibition of glucuronidation, any clinically relevant interactions caused by phase 2 metabolism are unlikely to occur. In a set of drug-drug interaction trials using paracetamol, naproxen, acetylsalicylic acid and probenecid, a possible influence of these active substances on the glucuronidation of tapentadol was investigated. The trials with probe active substances naproxen (500 mg twice daily for 2 days) and probenecid (500 mg twice daily for 2 days) showed increases in AUC of tapentadol by 17% and 57%, respectively. Overall, no clinically relevant effects on the serum concentrations of tapentadol were observed in these trials.

Furthermore, interaction trials of tapentadol with metoclopramide and omeprazole were conducted to investigate a possible influence of these active substances on the absorption of tapentadol. These trials also showed no clinically relevant effects on tapentadol serum concentrations.

In vitro studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur.

Plasma protein binding of tapentadol is low (approximately 20%). Therefore, the likelihood of pharmacokinetic drug-drug interactions by displacement from the protein binding site is low.

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. After intravenous dosing in rats reduced in utero survival was seen. In rats tapentadol caused increased mortality of the F_1 pups that were directly exposed via milk between days 1 and 4 post partum 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 is concluded that tapentadol is excreted via milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)
Citric acid monohydrate
Sucralose (E955)
Raspberry flavor (containing propylene glycol)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years
After first opening of the bottle, the solution should not be used for longer than six weeks.

6.4 Special precautions for storage

Unopened: This medicinal product does not require any special storage conditions.
After first opening: Store in an upright position.

6.5 Nature and contents of container

High density polyethylene (HDPE)-bottles sealed with aluminium foil liner and closed with a high density polyethylene (HDPE) / polypropylene (PP) child-resistant cap.

Each bottle of the oral solution is provided with an oral syringe and an adapter. The syringe is scaled in 0.25 milliliter increments with a minimum volume of 0.25 ml and a maximum volume of 5 ml.

100 ml bottles

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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Middlesex UB11 1BD
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8 MARKETING AUTHORISATION NUMBER

PA1189/008/010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th December 2012

10 DATE OF REVISION OF THE TEXT