ACORANIL 25mg/5ml Syrup

PL 20132/0002

UKPAR

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ACORANIL 25mg/5ml Syrup

PL 20132/0002

LAY SUMMARY

The MHRA today granted Acorus Therapeutics Limited Marketing Authorisation (licence) for the medicinal product Acoranil 25mg/5ml Syrup (PL 20132/0002). This is a prescription-only medicine (POM).

Acoranil Syrup contains 25mg imipramine (as hydrochloride) in every 5ml of syrup. Imipramine belongs to a class of medicines called tricyclic antidepressants and is used to treat depression and also to treat night time bed-wetting in children.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Acoranil Syrup outweigh the risks, hence Marketing Authorisation has been granted.

ACORANIL 25mg/5ml Syrup

PL 20132/0002

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisation for the medicinal product ACORANIL 25mg / 5ml Syrup (PL 20132/0002) to Acorus Therapeutics Limited on 19th March 2008. The product is prescription-only medicine.

This application was submitted as abridged application according to Article 10(1) of Directive 2001/83/EC, claiming essential similarity to Tofranil 25mg/5ml Syrup authorised to Novartis in the UK (PL 00101/0545) and first authorised in the EU in 1972.

Imipramine is a tricyclic antidepressant and has several pharmacological actions including alpha-adrenolytic, anti-histaminic, anticholinergic and 5HT-receptor blocking properties. However, the main therapeutic activity is believed to be inhibition of the neuronal re-uptake of noradrenaline and 5HT. Imipramine is a so-called 'mixed' re-uptake blocker, i.e. it inhibits the reuptake of NA and 5HT to about the same extent.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

INN: Imipramine hydrochloride

Chemical names: 5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f] azepine monohydrochloride

10,11-dihydro-N,N-dimethyl-5H-dibenz[b,f]-azepine-5-propanamine monohydrochloride

N-(γ-dimethylamonopropyl)iminodibenzyl mono- hydrochloride

5*H*-dibenz [*bf*]azepine-5-propanamine, 10,11-dihydro-*N*,*N*-dimethyl-monohydrochloride

CAS Number: 113-52-0

Molecular formula: $C_{19}H_{24}N_2HCl$

Molecular Weight: 316.9

Imipramine is a white or slightly yellow, odourless or practically odourless crystalline powder.

This is subject to DMF. Letter of access has been submitted.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Imipramine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 5 years for the drug substance when stored at 25°C in polythene bags inside aluminium laminate bags.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely beta cyclodextrin, sorbitol solution 70%, sodium saccharin, hydroxyethyl cellulose, propylene glycol, methyl paraben, propyl paraben, banana flavour and water.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of banana flavour which complies with in house specification.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

No overage of the active substance is included in this formulation.

Manufacture

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The product is packaged in Type III amber glass bottle with polypropylene child-resistant closure. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with storage conditions ‘Store below 25degree C’ and ‘Keep container tightly closed’ are proposed, which are satisfactory.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the

leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusion

It is recommended that Marketing Authorisation is granted for this application.

The requirements for essential similarity of the proposed and reference product have been met with respect to qualitative and quantitative content of the active substance and pharmaceutical form. It was not necessary to demonstrate bioequivalence.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for applications of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

Imipramine is one of the original tricyclic antidepressants, acting to inhibit the re-uptake of noradrenaline and serotonin (5HT) in about equal amounts.

2. BACKGROUND

Acorus Therapeutics Ltd have applied for this standard national application, cross-referring to Tofranil 25mg/5ml syrups marketed by Novartis, which was first authorised in August 1972, (PL 00101/0545).

3. INDICATIONS

Imipramine is indicated for the treatment of symptoms of depressive illness and, in children, the relief of nocturnal enuresis.

4. DOSE & DOSE SCHEDULE

The dose advice is fully in line with the SPC for the UK reference product.

5. TOXICOLOGY

No formal data is presented under this heading and none is required for this application.

6. CLINICAL PHARMACOLOGY

No formal data is presented under this heading and none is required for this application. The pharmacology of imipramine has been well understood for many years. The absence of a need for a bioavailability study is well addressed by the clinical expert.

7. EFFICACY

No formal data is presented under this heading and none is required for this application. The efficacy of imipramine is well recognised and has been so for many years.

8. SAFETY

The adverse events that can be expected are listed in the Summary of Product Characteristics and are consistent with those of the originator product.

9. EXPERT REPORTS

The applicant has submitted an expert report by an appropriately qualified physician.

10. PATIENT INFORMATION LEAFLET (PIL)

Satisfactory.

11. LABELLING

Satisfactory.

12. APPLICATION FORM (MAA)

Medically satisfactory

13. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is Satisfactory and is consistent with current cross-reference SPC.

14. DISCUSSION

Acorus Therapeutics Ltd has developed an imipramine syrup to replace Tofranil syrup that Novartis Pharmaceuticals UK Ltd is discontinuing. It is used in the treatment both of depression, and in children of 6 years and older, of nocturnal enuresis.

The clinical expert has provided a thorough review of the literature, including recent relevant references and, as a result, has made a number of sensible recommendations for additions to the SPC which will in turn impact the PIL.

15. MEDICAL CONCLUSION

Marketing Authorisation is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of ACORANIL 25mg / 5ml Syrup is well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No new data were submitted and none are required for applications of this type.

The SPC, PIL and labelling are satisfactory and consistent with that for reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ACORANIL Syrup is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.

ACORANIL 25MG/5ML SYRUP

PL 20132/0002

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 13th May 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 4th July 2003
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 15th October 2003, 24th August 2004, 1st December 2005 and the clinical dossier on 14th August 2003
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 12th February 2004, 18th May 2005 and 10th April 2006 and on the clinical dossier on the 12th February 2004
5	The applications were determined on 19th March 2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
ACORANIL 25mg / 5ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Imipramine hydrochloride (N-(γ-dimethylaminopropyl)-iminodibenzyl hydrochloride) 25mg / 5ml in a syrup formulation

Each 5ml of syrup also contains ;

Sorbitol (E420)	1500.0	mg
Methylhydroxy benzoate (E218)	6.85	mg
Propylhydroxy benzoate (E216)	0.57	mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Syrup

A clear colourless banana flavoured syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Symptoms of depressive illness. Relief of nocturnal enuresis in children.

4.2 Posology and method of administration
Depression:
Adults: 1 x 25mg up to three times daily, increasing stepwise to 150-200mg. This should be reached by the end of the first week and maintained until definite improvement has occurred. The subsequent maintenance dose should be individually determined by gradually reducing the dosage, usually to about 50-100mg daily.

In patients in hospital, i.e. severe cases, the dose may be increased to 100mg three times daily until a distinct improvement is seen. Again the subsequent maintenance dose should be determined individually by reducing the dosage, usually to about 100mg daily.

Elderly patients: Patients over 60 years of age may respond to lower doses of Acoranil than those recommended above. Treatment should be initiated with 10mg daily, gradually increasing to 30-50mg daily. The optimum dose should be reached after about 10 days and then continued until the end of treatment.

*Nocturnal Enuresis in Children:*Not for use in children under 6 years.
6 - 7 years (weight 20-25kg or 44-55lbs) 25mg
8 - 11 years (weight 25-35kg or 55-77lbs) 25 - 50mg
Over 11 years (weight 35-54kg or 77-119lbs) 50 - 75mg

A daily dosage of 2.5mg/kg should not be exceeded in children. The dose should be taken just before bedtime. The maximum period of treatment should not exceed three months and withdrawal should be gradual. Should a relapse occur, a further course of treatment should not be started until a full physical examination has been made.

4.3 Contraindications
Known hypersensitivity to imipramine, any of the excipients or cross-sensitivity to other tricyclic antidepressants of the dibenzazepine group. Recent myocardial infarction. Any degree of heart block or other cardiac arrhythmias, mania, severe liver disease, narrow angle glaucoma. Infants and children under 6 years old. Retention of urine. Concurrent use in patients receiving, or within 3 weeks of cessation of therapy with, monoamine oxidase

inhibitors. Concomitant treatment with selective, reversible MAO-A inhibitors such as moclobemide, is also contra-indicated.

4.4 Special warnings and precautions for use

Warnings

As improvement in depression may not occur for the first two to four weeks' treatment, patients should be closely monitored during this period.

Precautions

Tricyclic antidepressants are known to lower the convulsion threshold and Acoranil should therefore be used with extreme caution in patients with epilepsy and other predisposing factors, e.g. brain damage of varying aetiology, concomitant use of neuroleptics, withdrawal from alcohol or drugs with anticonvulsive properties (e.g. benzodiazepines). It appears that the occurrence of seizures is dose dependent.

Concomitant treatment of Acoranil and electroconvulsive therapy should only be resorted to under careful supervision.

Caution is called for when giving tricyclic antidepressants to patients with severe renal disease.

Caution is called for when giving tricyclic antidepressants to patients with tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), in whom they may provoke hypertensive crises.

Many patients with panic disorders experience intensified anxiety symptoms at the start of the treatment with antidepressants. This paradoxical initial increase in anxiety is most pronounced during the first few days of treatment and generally subsides within two weeks.

Caution is indicated in patients with hyperthyroidism or during concomitant treatment with thyroid preparations, since aggravation of unwanted cardiac effects may occur.

Before initiating treatment it is advisable to check the patient's blood pressure, because individuals with hypotension or a labile circulation may react to the drug with a fall in blood pressure.

Although changes in the white blood cell count have been reported with imipramine only in isolated cases, periodic blood cell counts and monitoring for symptoms such as fever and sore throat are called for, particularly during the first few months of therapy.

Periodic monitoring of hepatic enzyme levels is recommended in patients with liver disease. In elderly patients monitoring of cardiac function is indicated.

Because of its anticholinergic properties, imipramine should be used with caution in patients with a history of increased intra-ocular pressure, narrow angle glaucoma, or urinary retention (e.g. diseases of the prostate).

Caution is called for in patients with chronic constipation. Tricyclic antidepressants may cause paralytic ileus, particularly in the elderly and bedridden patients.

Before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving Acoranil. Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension (see interactions).

An increase in dental caries has been reported during long-term treatment with tricyclic antidepressants. Regular dental check-ups are therefore advisable during long-term treatment.

Decreased lacrimation and accumulation of mucoid secretions due to the anticholinergic properties of tricyclic antidepressants may cause damage to the corneal epithelium in patients with contact lenses.

Risk of suicide is inherent to severe depression and may persist until significant remission occurs. Patients posing a high suicide risk require close supervision.

Imipramine may cause anxiety, feelings of unrest, and hyperexcitation in agitated patients and patients with accompanying schizophrenic symptoms.

Activation of psychosis has occasionally been observed in schizophrenic patients receiving tricyclic antidepressants. Hypomanic or manic episodes have also been reported during a depressive phase in patients with cyclic affective disorders receiving treatment with a tricyclic antidepressant. In such cases it may be necessary to reduce the dosage of Acoranil or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with Acoranil may be resumed if required.

In predisposed and elderly patients, Acoranil may, particularly at night, provoke pharmacogenic (delirious) psychoses, which disappear without treatment within a few days of withdrawing the drug. Agitation, confusion and postural hypotension may occur. Abrupt withdrawal should be avoided because of possible adverse reactions (see side effects).

Behavioural changes may occur in children receiving Acoranil for treatment of nocturnal enuresis.

Acoranil contains sorbitol so may be unsuitable for patients with hereditary fructose intolerance

4.5 Interaction with other medicinal products and other forms of interaction

MAO inhibitors: Do not give Acoranil for at least 3 weeks after discontinuation of treatment with MAO inhibitors (there is a risk of severe symptoms such as hypertensive crisis, hyperpyrexia, myoclonus, agitation, seizures, delirium and coma). The same applies when giving a MAO inhibitor after previous treatment with Acoranil. In both instances Acoranil or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored. There is evidence to suggest that tricyclic antidepressants may be given as little as 24 hours after a reversible MAO inhibitor such as moclobemide, but the 3 week wash-out period must be observed if the MAO inhibitor is given after a tricyclic antidepressant has been used.

Selective serotonin reuptake inhibitors: Co-medication may lead to additive effects on the serotonergic system. Fluvoxetine and fluvoxamine may also increase plasma concentrations of imipramine, with corresponding adverse effects, resulting in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold and seizures.

CNS depressants: Tricyclic antidepressants may also increase the effect of alcohol and central depressant drugs (e.g. barbiturates, benzodiazepines or general anaesthetics).

Alprazolam and disulfiram: It may be necessary to reduce the dosage of imipramine if it is administered concomitantly with aprazolam or disulfiram.

Neuroleptics: Co-medication may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.

Adrenergic neurone blockers: Imipramine may diminish or abolish the antihypertensive effects of guanethidine, betanidine, reserpine, clonidine and alpha-methyldopa. Patients requiring co-medication for hypertension should therefore be given antihypertensives of a different type (e.g. diuretics, vasodilators, or beta blockers).

Anticoagulants: Tricyclic antidepressants may potentiate the anti-coagulant effect of coumarin drugs by inhibiting hepatic metabolism of these anticoagulants. Careful monitoring of plasma prothrombin is therefore advised.

Anticholinergic agents: Tricyclic antidepressants may potentiate the effects of these drugs (e.g. phenothiazine, antiparkinsonian agents, antihistamines, atropine, biperiden) on the eye, central nervous system, bowel and bladder.

Sympathomimetic drugs: Imipramine may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine (e.g. as contained in local anaesthetic preparations and nasal decongestants).

Quinidine: Tricyclic antidepressants should not be employed in combination with anti-arrhythmic agents of the quinidine type.

Liver enzyme inducers: Drugs that activate the hepatic mono-oxygenase enzyme system (e.g. barbiturates, carbamazepine, phenytoin, nicotine, and oral contraceptives) may accelerate the metabolism and lower plasma concentrations of imipramine, resulting in decreased efficacy. Plasma levels of phenytoin and carbamazepine may increase, with corresponding adverse effects. It may be necessary to adjust the dosage of these drugs.

Cimetidine, methylphenidate, terbinafine, amfebutamone: These drugs may increase the plasma concentrations of tricyclic antidepressants, whose dosage should therefore be reduced.

Estrogens: There is evidence that estrogens can sometimes paradoxically reduce the effects of imipramine yet at the same time cause imipramine toxicity.

4.6 Pregnancy and lactation

Use During Pregnancy and Lactation: There is no evidence of the safety of the drug in human pregnancy. There have been isolated reports of a possible connection between the use of tricyclic antidepressants and adverse effects (developmental disorders) on the foetus; treatment with Acoranil should be avoided during pregnancy, unless the anticipated benefits justify the potential risk to the foetus.

Neonates whose mothers had taken imipramine up until delivery have developed dyspnoea, lethargy, colic, irritability, hypotension or hypertension, tremor or spasms, during the first few hours or days. Acoranil should if possible be gradually withdrawn at least 7 weeks before the calculated date of confinement.

The active substance of Acoranil, imipramine, and its metabolite, desmethylimipramine, pass into the breast milk in small quantities. Acoranil should be gradually withdrawn or the mother advised to cease breast-feeding.

4.7 Effects on ability to drive and use machines

Patients receiving Acoranil should be warned that blurred vision, drowsiness and other CNS symptoms (see Side Effects) may occur, in which case they should not drive, operate machinery, or do anything which may require alertness or quick actions. Patients should also be warned that alcohol or other drugs may potentiate these effects, (see Interactions).

4.8 Undesirable effects

If severe neurological or psychiatric reactions occur, Acoranil should be withdrawn.
Elderly patients are particularly sensitive to anticholinergic, neurological, psychiatric, or cardiovascular effects. Their ability to metabolise and eliminate drugs may be reduced, leading to a risk of elevated plasma concentrations at therapeutic doses.

The following side-effects, although not necessarily observed with imipramine, have occurred with tricyclic antidepressants.
(The following frequency estimates are used: frequently > 10%, occasionally >1-10%, rarely >0.001-1%, isolated cases < 0.001%)

Central Nervous System:
Psychiatric Effects:
Occasionally: fatigue, drowsiness, restlessness, delirium, confusion, disorientation and hallucinations (particularly in geriatric patients and those suffering from Parkinson's disease),

increased anxiety, agitation, sleep disturbances, swings from depression to hypomania or mania.
Rarely: activation of psychotic symptoms.
Isolated cases: aggressiveness.

Neurological Effects:
Frequently: tremor.
Occasionally: paraesthesiae, headache, dizziness.
Rarely: epileptic seizures.
Isolated cases of EEG changes, myoclonus, weakness, extrapyramidal symptoms, ataxia, speech disorders, drug fever.

Cardiovascular System:
Frequently: sinus tachycardia and clinically irrelevant ECG changes (T and ST changes) in patients of normal cardiac status, postural hypotension.
Occasionally: arrhythmias, conduction disorders (widening of QRS complex and PR interval, bundle-branch block), palpitations.
Isolated cases of increased blood pressure, cardiac decompensation, peripheral vasospastic reactions.

Anticholinergic Effects:
Frequently: dry mouth, sweating, constipation, disorders of visual accommodation, blurred vision, hot flushes.
Occasionally: disturbances of micturition.
Isolated cases of mydriasis, glaucoma, paralytic ileus.

Gastro-Intestinal Tract:
Occasionally: nausea, vomiting, anorexia.
Isolated cases of stomatitis, tongue lesions, abdominal disorders.

Hepatic Effects:
Occasionally: elevated transaminases.
Isolated cases of hepatitis with or without jaundice.

Skin:
Occasionally: allergic skin reactions (skin rash, urticaria).
Isolated cases of oedema (local or generalised), photosensitivity, hyperpigmentation, pruritus, petechiae, hair loss.

Endocrine System and Metabolism:
Frequently: weight gain.
Occasionally: disturbances of libido, impotency or abnormal ejaculation.
Isolated cases of enlarged mammary glands, galactorrhoea, SIADH (syndrome of inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar, weight loss.

Hypersensitivity:
Isolated cases of allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension.

Blood:
Isolated cases of eosinophilia, leucopenia, agranulocytosis, thrombocytopenia and purpura.

Sense organs
Tinnitus.

Miscellaneous:
Occasional withdrawal symptoms following abrupt discontinuation of treatment: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness and anxiety. Contains 1.5g of sorbitol per 5ml spoonful so may cause stomach upset and diarrhoea, particularly at high doses.

4.9 Overdose

The signs and symptoms of overdose with imipramine are similar to those reported with other tricyclic antidepressants. Cardiac abnormalities and neurological disturbances are the main complications. In children, accidental ingestion of any amount should be regarded as serious and potentially fatal.

Signs and Symptoms: Symptoms generally appear within 4 hours of ingestion and reach a maximum severity after 24 hours. Owing to delayed absorption (increased anticholinergic effect due to overdose), long half-life and enterohepatic recycling of the drug, the patient may be at risk for up to 4-6 days.

The following may be encountered:

Central nervous system: drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity, athetoid and choreiform movements, convulsions.

Cardiovascular System: Hypotension, tachycardia, arrhythmia, conduction disorders, heart failure; in very rare cases, cardiac arrest.

In addition, respiratory depression, cyanosis, shock, vomiting, fever, hydriasis, sweating and oliguria or anuria may occur.

Treatment: There is no specific antidote and treatment is essentially symptomatic and supportive. Anyone suspected of receiving an overdose of imipramine, particularly children, should be admitted to hospital and kept under close surveillance for at least 72 hours.

Perform gastric lavage or induce vomiting as soon as possible if the patient is fully conscious. If the patient has impaired consciousness, secure the airway with a cuffed endotracheal tube before beginning lavage, and do not induce vomiting. These measures are recommended for up to 12 hours or even longer after the overdose, since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help reduce drug absorption.

Treatment of symptoms is based on modern methods of intensive care, with continuous monitoring of cardiac function, blood gases and electrolytes, and if necessary emergency measures such as:
- anticonvulsive therapy,
- artificial respiration,
- insertion of a temporary cardiac pacemaker,
- plasma expander, dopamine or dobutamine administered by intravenous drip,
- resuscitation.

Since it has been reported that physostigmine may cause severe bradycardia, asystole and seizures, its use is not recommended in cases of overdosage with imipramine. Haemodialysis or peritoneal dialysis are ineffective because of the low plasma concentrations of imipramine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tricyclic antidepressant. Noradrenaline (NA) and serotonin (5HT) re-uptake inhibitor. ATC Code N06A A02

Imipramine is a tricyclic antidepressant and has several pharmacological actions including alpha-adrenolytic, anti-histaminic, anticholinergic and 5HT-receptor blocking properties. However, the main therapeutic activity is believed to be inhibition of the neuronal re-uptake of noradrenaline and 5HT. Imipramine is a so-called 'mixed' re-uptake blocker, i.e. it inhibits the reuptake of NA and 5HT to about the same extent.

5.2 Pharmacokinetic properties

Absorption: Imipramine is absorbed quickly and completely following oral administration. The intake of food has no effect on its absorption and bioavailability. During its first passage through the liver, orally administered imipramine becomes partly converted to desmethylimipramine, a metabolite which also exhibits antidepressant activity.

During oral administration of 50mg 3 times daily for 10 days, the mean steady-state plasma concentrations of imipramine and desmethylimipramine were 33-85ng/ml and 43-109ng/ml respectively. Owing to lower clearance in the plasma, resulting in increased systemic availability, elderly patients require lower doses of imipramine than patients in intermediate age groups. Renal impairment is not expected to have any influence on the kinetics of unchanged imipramine and its desmethyl metabolite since both are excreted only in small amounts by the kidneys.

Distribution: About 86% of imipramine binds to plasma proteins. Concentrations of imipramine in the cerebrospinal fluid and the plasma are highly correlated. The mean distribution volume is about 21L/kg.

Imipramine and its metabolite desmethylimipramine both pass into breast milk in concentrations similar to those found in the plasma.

Biotransformation: Imipramine is extensively metabolised in the liver. It is cleared mainly by demethylation and to a lesser extent by hydroxylation. Both metabolic pathways are under genetic control.

Elimination: Imipramine is eliminated from the blood with a mean half-life of about 19 hours. About 80% is excreted in the urine and about 20% in the faeces, mainly in the form of inactive metabolites. Urinary excretion of unchanged imipramine and of the active metabolite desmethylimipramine is about 5% and 6%, respectively. Only small quantities of these are excreted in the faeces.

Characteristics in patients: Owing to reduced metabolic clearance, plasma concentrations of imipramine are higher in elderly patients than in younger patients.

In children the mean clearance and elimination half-life does not differ significantly from adult controls but the between-patient variability is high.

In patients with severe renal impairment, no change occurs in renal excretion of imipramine and its biologically active unconjugated metabolites. However, steady-state plasma concentrations of the conjugated metabolites which are considered to be biologically inactive, are elevated. The clinical significance of this finding is not known.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betacyclodextrin (E459)
Sorbitol (E420)
Sodium saccharin (E954)
Hydroxyethylcellulose,
Methyl paraben (E218)
Propyl paraben (E216)
Propylene glycol (E1520)
Banana flavour (containing nature identical flavouring substances and mono-propylene glycol as carrier)
Purified water.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years unopened.
30 days once opened.

6.4 Special precautions for storage
Store below 25°C. Keep containers tightly closed.

6.5 Nature and contents of container
Acoranil is supplied in 150 ml round Type III amber glass bottles with a white plastic child resistant clic-loc cap.

6.6 Special precautions for disposal and other handling
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Acorus Therapeutics Limited,
Office Village,
Chester Business Park,
Chester,
CH4 9QZ,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20132/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/03/2008

10 DATE OF REVISION OF THE TEXT
19/03/2008

PATIENT INFORMATION LEAFLET

Acoranil Syrup
Imipramine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions please ask your doctor or pharmacist.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

1. What is Acoranil Syrup and what is it used for?

Acoranil Syrup contains 25mg imipramine (as hydrochloride) in every 5 ml of syrup. Imipramine belongs to a class of medicines called tricyclic antidepressants and is used to treat depression and also to treat nighttime bed-wetting in children.
This medicine also contains betacyclodextrin (E459), sorbitol (E420), saccharin sodium (E954), hydroxyethylcellulose, propylene glycol (E1520), banana flavour, methylhydroxybenzoate (E218), propylhydroxybenzoate (E216), and water.

Acoranil Syrup comes in bottles of 150ml and is manufactured by Dales Pharmaceuticals (Trading division of Dechra Ltd), Snaygill Industrial Estate, Keighley Road, Skipton, North Yorkshire, BD23 2RW
The product licence holder is Acorus Therapeutics Ltd, Office Village, Chester Business Park, Chester CH4 9QZ, UK.

2. Before you take Acoranil Syrup

Do not take this medicine if you answer YES to any of these questions:
- Have you ever had a rash or other possible allergic reaction whilst taking anti-depressants?
- Are you allergic to any of the ingredients?
- Do you suffer from any serious heart, liver or kidney disease?
- Do you suffer from glaucoma (increased eye pressure)?
- Do you have difficulty in passing water?
- Do you suffer from any mental illness other than depression?
- Have you had a heart attack within the past three months?
- Are you taking or have you recently taken any other medicines for depression (particularly monoamine oxidase inhibitors [MAOIs])?

Instead tell your doctor what questions you have answered YES to and only start to take Acoranil Syrup if your doctor says it is okay to continue.

If you answer YES to any of the following questions, tell your doctor or pharmacist.
- Do you suffer from epilepsy (fits)?
- Do you have a tumour of the adrenal gland (for example, phaeochromocytoma or neuroblastoma)?
- Do you have an overactive thyroid?
- Do you suffer from constipation?
- Are you pregnant, planning to become pregnant or breast-feeding?
- Do you have an intolerance to some sugars?

Are you taking any of the following?
- Medicines for high blood pressure or heart disease?
- Medicines for colds, sinus problems, hay fever or allergies?
- Oral contraceptives or oestrogens (e.g. hormone replacement therapy [HRT])?
- Cimetidine (an anti-ulcer drug)?
- Methylphenidate (a medicine used to treat behavioral disorders in children)?
- Barbiturates, tranquillizers or sleeping tablets?
- Anticoagulants (blood-thinning tablets like warfarin)?

If you answer YES to any of these questions, tell your doctor or pharmacist. These medicines may interact with Acoranil so it may be necessary to change the dose or stop one of the medicines.

Other warnings
- Be careful when drinking alcohol – it may affect you more than usual.
- If you feel dizzy or sleepy when you take this medicine, do not drive or work machinery until these effects have worn off.
- Whilst you are taking Acoranil, your doctor may want to carry out routine tests (blood, heart and liver tests) from time to time.

- This medicine can cause dry mouth so there may be an increased chance of tooth decay. You should have regular dental check-ups whilst taking Acoranil.
- Tell your doctor that you are taking Acoranil if you are planning to have an operation of any kind.
- Children under 6 years old should not take this medicine.

3. How to take your medicine

You must take it as instructed by your doctor. The usual dosages are given below - if your dose is different, do not change it without talking to your doctor first.

Depression:

Adults: At first, one spoonful (25mg) one to three times a day. Your doctor may increase your dose gradually as needed. However, the dose is usually not more than 6 to 8 spoonfuls (150-200mg) a day unless you are in hospital.
Elderly: Lower doses may be used. At first 2 ml (10 mg) a day increasing gradually to one to two spoonfuls (25-50mg) a day if needed.

Nighttime Bed-wetting:

Children: 1 – 3 spoonfuls (25mg-75 mg) a day at bedtime depending on the age and weight of the child. Treatment with Acoranil should be checked after 3 months.

If you are not sure how much medicine to take, ask your doctor or pharmacist.

Keep taking your medicine until your doctor tells you to stop. Do not stop suddenly because you do not feel any better. This medicine may take up to four weeks to work. If you need to stop treatment, your doctor will tell you how to reduce the dose gradually. This is to help prevent unwanted effects such as headache, sickness, stomach upset, diarrhoea, sleeplessness, nervousness and anxiety.

- It is important to take your medicine at the right times. If you forget to take a dose, take the next dose at the usual time. DO NOT take a double dose.
- **If you accidentally take too much Acoranil Syrup, tell your doctor at once or contact your hospital casualty department. Overdosage in children is serious and could be potentially fatal.**

4. Possible side-effects

This medicine sometimes causes unwanted effects in some people. The most common side-effects are:
Drowsiness, tiredness, dizziness, restlessness, dry mouth, mild blurring of vision, headache, nausea, hot flushes, sweating, constipation, trembling, weight gain.
At the start of treatment, Acoranil may also increase your feelings of anxiety.

These effects are often mild and may go away during treatment. If they are severe or last for more than a few days, tell your doctor.

You are unlikely to experience any of the following side-effects but if you do - see your doctor as soon as possible:
Any yellowing of your skin or the whites of your eyes, skin rash or itching, sore throat or fever, loss of balance, eye pain, muscle weakness or stiffness, muscle spasm, difficulty in passing water, difficulty in speaking, hair loss, shortness of breath, swelling of the breasts and discharge of milk, fast or irregular heartbeat, increased sensitivity to sunlight, red or brownish spots on skin, sexual difficulties, fits, confusion or delirium, ringing in the ears, sleep disturbances, mood changes, aggression, raised blood pressure, lightheadedness (especially when getting up from lying or sitting position), vomiting, anorexia, weight loss, hallucinations, paralytic ileus, change in blood sugar levels.

This medicine contains 1.5g of sorbitol per 5ml spoonful, which has a calorific value of 2.6 kcal/g and may have a mild laxative effect. Propylhydroxybenzoate (E216) and methylhydroxybenzoate (E218) may cause allergic reactions (possibly delayed).

If you notice any other side-effects not mentioned in this leaflet, tell your doctor.

5. Storing Acoranil Syrup

- Keep the bottle tightly closed and in its carton when not in use.
- Keep the medicine in a cool (below 25°C) place out of the sight and reach of children.
- The expiry date for this medicine is given on the carton and the bottle. Do not take after this date.
- Do not use one month after first opening. Return any unused medicine to your pharmacist.

This leaflet was approved: ?????????
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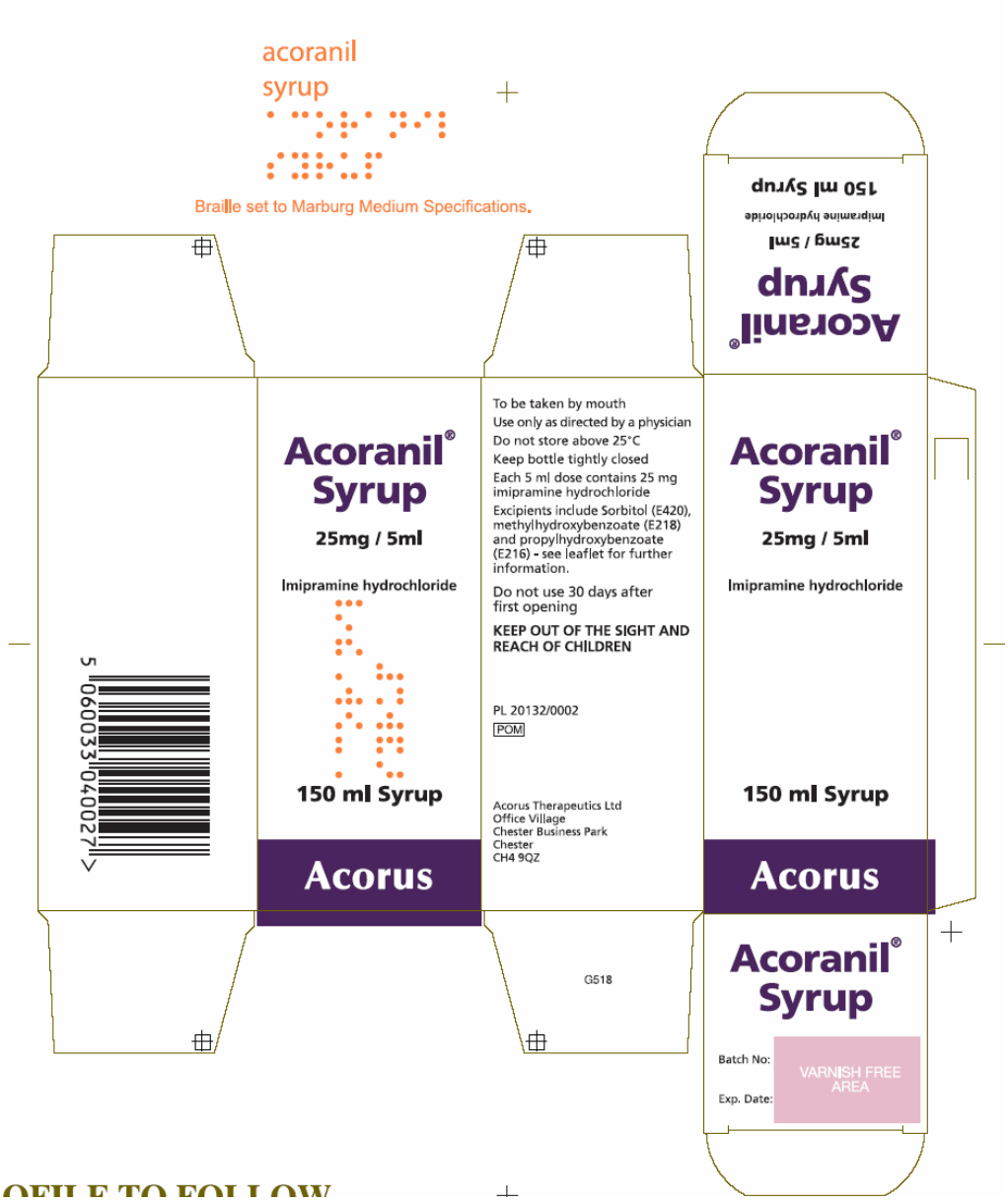
LABELLING



PROFILE TO FOLLOW


To be taken by mouth
Use only as directed by a physician
Do not store above 25°C
Keep bottle tightly closed
Each 5 ml dose contains 25 mg imipramine hydrochloride
Excipients include E420, E218 and E216 – see leaflet for further information.
Do not use 30 days after first opening
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
POM
PL 20132/0002
E1209
Acoranil®
Syrup
Imipramine hydrochloride
25mg / 5ml
150 ml Syrup
VARNISH FREE AREA
Batch No:
Exp. Date:
Acorus
Acorus Therapeutics Ltd., Office Village, Chester Business Park, Chester CH4 9QZ, UK