Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

TETMODIS 25MG TABLETS
(TETRABENAZINE)

UK/H/1816/001/DC
UK Licence No: PL 30414/0005

ORPHA-DEVEL HANDELS UND VERTRIEBS GMBH

LAY SUMMARY

On 20th July 2010, the UK granted Orpha-Devel Handels und Vertriebs GmbH a Marketing Authorisation (licence) for Tetmodis 25mg tablets (PL 30414/0005; UK/H/1816/001/DC). These are prescription-only medicines (POM) for the treatment of diseases causing jerky, irregular, uncontrollable movements (hyperkinetic motor disorders with Huntington's chorea).

The active ingredient in this medicine is tetrabenazine. This belongs to the group of medicines that treat disorders of the nervous system.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Tetmodis 25mg tablets outweigh the risks; hence this Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Product Name	Tetmodis 25mg tablets
Type of Application	Generic application, Article 10.1
Active Substance	Tetrabenazine
Form	Tablets
Strength	25mg
MA Holder	Orpha-Devel Handels und Vertriebs GmbH, 3002 Purkersdorf, Austria
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Austria, Belgium, Bulgaria, the Czech Republic, Denmark, Estonia, Germany, Greece, Finland, France, Hungary, Ireland, Italy, Latvia, Lithuania, the Netherlands, Poland, Portugal, Romania, Spain, Slovenia, the Slovak Republic, Sweden
Procedure Number	UK/H/1816/001/DC
End of Procedure	Day 210 – 16th June 2010

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Tetmodis 25 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 25 mg Tetrabenazine.
Each tablet contains 60.8 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

Yellow, round, flat, with a breaking score on one-side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Tetmodis is indicated for hyperkinetic motor disorders with Huntington's chorea.

4.2 Posology and method of administration
The tablets are for oral use. The therapy should be supervised by a doctor experienced in treating hyperkinetic disorders.

Adults
Huntington's chorea
Dosage and administration are individual in each patient and therefore only a guide is given.

An initial starting dose of 12.5 mg/day one to three times a day is recommended. This can be increased every three or four days by 12.5 mg until the optimal effect is observed or up to the occurence of intolerance effects (sedation, Parkinsonism, depression).

The maximum daily dose is 200 mg a day.

If there is no improvement at the maximum dose in seven days, it is unlikely that the compound will be of benefit to the patient, either by increasing the dose or by extending the duration of treatment.

Elderly
No specific studies have been performed in the elderly, but tetrabenazine has been administered to elderly patients in standard dosage without apparent ill effect. Parkinson-like adverse reactions are quite common in these patients and could be dose-limiting.

Children
No adequate controlled studies have been performed in children. The treatment is not recommended in children.

Patients with hepatic impairment
In patients with mild and moderate hepatic impairment half the initial dose and a slower up-titration of the dose is recommended. Patients with severe hepatic impairment have not been studied, therefore additional caution is advised in these patients (see also section 4.4 and 5.2).

Patients with renal impairment
No studies have been performed in patients with renal impairment. Caution is advised in the treatment of these patients.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients
- Tetrabenazine can block the action of reserpine. Thus these substances should not be taken

concomitantly.
- Use of monoamine oxidase inhibitors
- Presence of a hypokinetic-rigid-syndrome (Parkinsonism)
- Depression
- Breast feeding
- Pheochromocytoma
- Pro-lactin-dependent tumours, e.g. pituitary or breast cancer

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

It is known that dose dependent adverse events such as sedation, depression and the occurrence of a hypokinetic-rigid-syndrome (Parkinsonism) are possible. In such a case, the dose should be reduced and discontinuation of tetrabenazine be considered if events do not resolve.

MAO-inhibitors are contraindicated (see section 4.3) and should be stopped 14 days before the treatment with tetrabenazine starts.

Tetmodis should be used with caution in patients with hepatic impairment (see section 4.2).
A neuroleptic malignant syndrome has been described under the use of tetrabenazine and after abrupt withdrawal.

Neuroleptic malignant syndrome is a rare complication of tetrabenazine therapy. Neuroleptic Malignant Syndrome most often occurs early in treatment, in response to changes in dose or after prolonged treatment. The main symptoms of this condition are mental changes, rigidity, hyperthermia, autonomic dysfunction (sweating and fluctuations in blood pressure) and elevated creatinine phosphokinase levels. If Neuroleptic Malignant syndrome is suspected Tetrabenazine should be withdrawn immediately and appropriate treatment initiated.

Tetrabenazine causes a small increase (up to 8msec) in the corrected QT interval. Tetrabenazine should be used with caution in combination with other drugs known to prolong QTc and in patients with congenital long QT syndromes and a history of cardiac arrythmias (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Tetmodis should not be used concomitantly with reserpine, MAO inhibitors.

Levodopa should be administered with caution in the presence of Tetmodis.

Concomitant use with tricyclic antidepressants, alcohol, CYP2D6 inhibitors, opioids, beta blocking agents, antihypertensive drugs, hypnotics and neuroleptics is not recommended.

No interaction studies with tetrabenazine have been performed in vivo, and metabolising enzymes are partly unknown. In vitro studies indicate that tetrabenazine may be a CYP2D6 inhibitor and therefore cause increased plasma concentrations of medicinal products metabolised by CYP2D6.

Inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine, terbinafine, moclobemide and quinidine) may result in increased plasma concentrations of the active metabolite dihydrotetrabenazine, why they should only be combined with caution. A reduction of the tetrabenazine dose may be necessary.

Tetrabenazine should be used with caution with drugs known to prolong QTc including antipsychotic medications (e.g. chlorpromazine, thioridazine), antibiotics (e.g. gatifloxacin, moxifloxacin) and Class IA and III antiarrythmic medications (e.g. quinidine, procainamide, amiodarone, sotalol).

4.6 Pregnancy and lactation

Pregnancy
Animal studies are insufficient with respect to effects on pregnancy, embryofetal development, birth, or development post partum (see section 5.3). There are no adequate data from the use of tetrabenazine in pregnant women and the potential risk for humans is unknown. Tetmodis should not be used during pregnancy unless no other treatment is available.

Lactation
Tetrabenazine is contraindicated during lactation (see section 4.3). Breast-feeding must be stopped, if treatment with tetrabenazine is necessary.

4.7 Effects on ability to drive and use machines
Patients should be advised that Tetmodis may cause drowsiness and therefore may modify their performance at skilled tasks (driving ability, operation of machinery, etc.) to a varying degree, depending on dose and individual susceptibility.

4.8 Undesirable effects
The following undesirable effects are ranked according to system organ class and to their frequency:
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)

Psychiatric disorders
Very common: depression,
Common: anxiety, insomnia, confusion

Nervous system disorders
Very common: drowsiness (with higher dosages), Parkinson-like syndrome (with higher dosages)
Uncommon: altered levels of consciousness
Rare: Neuroleptic malignant syndrome (NMS) (see Section 4.4)

Vascular disorders
Common: Hypotension

Gastrointestinal disorders
Common: dysphagia, nausea, vomiting, diarrhoea, constipation

Musculoskeletal and connective tissue disorders
Uncommon: severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction
Very rare: Skeletal muscle damage

General disorders and administration site conditions
Uncommon: hyperthermia

For the following side-effects, it is not possible to estimate the incidence from available data:
Psychiatric disorders: disorientation, nervousness
Nervous system disorders: ataxia, akathisia, dystonia, dizziness, amnesia
Vascular disorders: bradycardia, epigastric pain, dry mouth

4.9 Overdose
Signs and symptoms of overdosage may include drowsiness, sweating, hypotension and hypothermia. Treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other nervous system drugs, ATC code: N07XX06

The central effects of Tetmodis closely resemble those of Reserpine, but it differs from the latter in having less peripheral activity and being much shorter acting.

Animal studies have shown that tetrabenazine disturbs the metabolism of biogenic amines, for instance that of serotonin and noradrenaline, and that this activity is limited to the brain. The supposition is that this effect of tetrabenazine on amines in the brain explains the clinical effects in the brain. Tetrabenazine inhibits the re-uptake of monoamines in the neuroterminal of the presynaptic neurons of the central nervous system. This results in a depletion of monoamines, including dopamine. Dopamine depletion results in hypokinesis leading to a reduction in chorea severity. Tetrabenazine inhibits the re-uptake of monoamines in synaptic nerve terminals by a reversible and short-term binding to the vesicular monoamine transporter (VMAT). VMAT2 transports monoamines especially in peripheral and central neurons, while VMAT1 regulates the transport in peripheral chromaffine tissues. Tetrabenazine has a higher affinity for VMAT2 than for VMAT1. Thus, tetrabenazine has a short, hardly peripheral effect.

5.2 Pharmacokinetic properties

Tetrabenazine has a low and erratic bioavailability. It appears to be extensively metabolised by first-pass metabolism. The major metabolite, hydroxytetrabenazine, is formed by reduction. Little unchanged Tetrabenazine can be detected in the urine. Since hydroxytetrabenazine is reported to be as active as Tetrabenazine in depleting brain amines, it is likely that this is the major therapeutic agent.

Special populations

Hepatic impairment

Mild and moderate hepatic impairment increases the exposure and prolongs the half-lives of tetrabenazine and hydroxytetrabenazine (4 patients with Child Pugh score 5-6 and 1 patient with Child Pugh score 9.) Severe hepatic impairment has not been studied.

5.3 Preclinical safety data

In repeat-dose toxicity studies, the effects observed with orally administered tetrabenazine were related to depletion of central stores of monoamines. Common symptoms were hypoactivity, lethargy, strabismus, or closed eyes. Primarily pharmacological effects such as sedation were observed and considered dose limiting.

The genotoxic potential of tetrabenazine has been studied using a series of conventional tests. In vitro, tetrabenazine was negative for point mutations and positive for chromosomal aberrations in Chinese hamster ovary cells, at cytotoxic concentrations only. Tetrabenazine was not genotoxic in an in vivo chromosomal aberration test; however, carcinogenicity studies have not been performed.

Studies to investigate the effects on fertility have not been conducted. Tetrabenazine was not embryotoxic or teratogenic in the rabbit; however, the observed systemic exposure was lower than that observed clinically. The potential embryotoxic and teratogenic effects were also insufficiently studied in the rat. In a peri/postnatal study in the rat, increased neonatal mortality was observed, the cause of which is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch
Lactose monohydrate
Talc
Iron oxide yellow E172
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

White round high-density polyethylene (HDPE) tablet container with a child-resistant, tamper-evident polypropylene (PP) screw cap with mounted desiccant containing 112 tablets.

6.6 Special precautions for disposal and other handling
No special requirements

7 MARKETING AUTHORISATION HOLDER
Orpha-Devel Handels und Vertriebs GmbH
3002 Purkersdorf, Austria

8 MARKETING AUTHORISATION NUMBER(S)
PL 30414/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/07/2010

10 DATE OF REVISION OF THE TEXT
20/07/2010

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tetmodis 25 mg tablets

Tetrabenazine

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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT TETMODIS IS AND WHAT IT IS USED FOR

Tetmodis is a medicine belonging to the group treating disorders of the nervous system.
Tetmodis is used for the treatment of diseases causing jerky, irregular, uncontrollable movements (hyperkinetic motor disorders with Huntington's chorea).

2. BEFORE YOU TAKE TETMODIS

Do not take Tetmodis
- if you are allergic (hypersensitive) to tetrabenazine or any of the other ingredients of Tetmodis 25 mg tablets.
- if you use reserpine (medicine to control high blood pressure and treat psychotic states).
- if you use MAO inhibitors (medicine to treat depression)
- if you suffer from Parkinson-like symptoms
- if you have a depression
- if you are breast-feeding
- if you suffer from pheochromocytoma (tumour of the adrenal gland)
- If you suffer from pro-lactin-dependent tumours, e.g. pituitary or breast cancer

Take special care with Tetmodis
- if you are suffering from mild to severe hepatic impairment.
- if you have a heart condition known as long QT syndrome or if you have or have had problems with your heart rhythm.
- if you start to have mental changes such as confusion or hallucinations, or develop stiffness in your muscles and a temperature, you may be developing a condition called Neuroleptic Malignant Syndrome. If you have these symptoms please contact your doctor straight away.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Take special care if you use Tetmodis together with Levodopa (a medicine used to treat Parkinson's disease). Do not use Tetmodis together with reserpine. Treatment with MAO inhibitors should be stopped 14 days before the treatment with tetrabenazine starts.
It is not recommended to use this medicine with certain types of antidepressants, alcohol,opioids, beta blockers, antihypertensive drugs (medicine to treat high blood pressure), hypnotics and neuroleptics (medicine to treat psychotic disorders).
Inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine, terbinafine, moclobemide and quinidine) may result in increased plasma concentrations of the active metabolite dihydrotetrabenazine, why they should only be combined with caution. A reduction of the tetrabenazine dose may be necessary.
Take special care if you use Tetmodis together with drugs known to prolong the QTc interval in the ECG, including some drug used to treat mental health conditions (neuroleptics), certain antibiotics (e.g. gatifloxacin, moxifloxacin) and some drugs used to treat problems with heart rhythm conditions (e.g. quinidine, procainamide, amiodarone, sotalol).

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Your doctor will decide after taking all risks and benefits into account, if you may use Tetmodis during pregnancy. Tetmodis must not be taken by breast feeding mothers.

Driving and using machines
Tetmodis may cause drowsiness and therefore may modify your performance at driving and using machines to a varying degree, depending on the dose and individual susceptibility.

Important information about some of the ingredients of Tetmodis
These tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE TETMODIS

Always take Tetmodis exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults
Huntington's chorea
The recommended starting dose is half a tablet (12.5 mg) one to three times a day. This can be increased every three or four days by half a tablet until the optimal effect is observed or up to the occurrence of intolerance effects (sedation, Parkinsonism, depression).
The maximum daily dose is 8 tablets (200 mg) a day.
If you have taken the maximum dose for a period of seven days and your condition has not improved, it is unlikely that the medicinal product will be of benefit to you.

The elderly
The standard dosage has been administered to elderly patients without apparent side effects. However, Parkinson-like side effects are common.

Children
The treatment is not recommended in children.

Patients with hepatic disorder
Patients with mild to moderate hepatic disorders should start with half a tablet a day. For patients with severe hepatic disorders, additional caution is necessary.

Patient with renal disorder
Tetmodis is not recommended for use in this patient group.

Swallow the tablet(s) with water or another non-

alcoholic drink.

If you take more Tetmodis than you should
If you take more Tetmodis than you should, you may develop drowsiness, sweating, low blood pressure, and extremely low body temperature (hypothermia). Your doctor will treat the signs.

If you forget to take Tetmodis
If you forget to take one dose, you should never make up for the missing dose by doubling it at the next time. Instead you should simply continue with the next dose when it is due.

If you stop taking Tetmodis
Do not stop taking Tetmodis unless your doctor tells you to. A neuroleptic malignant syndrome has been described after abrupt withdrawal of tetrabenazine.

If you have any further question on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tetmodis can cause side effects, although not everybody gets them.

The following undesirable effects are ranked according to system organ class and to their frequency:

very common:	affects more than 1 user in 10
common:	affects 1 to 10 users in 100
uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Very common:
Drowsiness (with higher dosages), depression, Parkinson-like syndrome (uncontrollable movements of the hands, arms, legs and head, with higher dosages)

Common:
Confusion, anxiety, sleeplessness, low blood pressure, dysphagia (difficulty in swallowing), nausea, vomiting, diarrhoea, obstipation

Uncommon:
Mental changes such as confusion or hallucinations, muscular rigidity, fever, autonomic dysfunction

Rare:
Neuroleptic malignant syndrome (NMS) (neurological disorder)

Very rare:
Skeletal muscle damage

For the following side-effects, it is not possible to estimate the incidence from available data:
Disorientation, nervousness, ataxia, akathisia, dystonia, dizziness, amnesia, bradycardia, epigastric pain, dry mouth

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TETMODIS

Keep out of the reach and sight of children.

Do not use Tetmodis after the expiry date which is stated on the bottle and carton. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

This medicinal product does not require any special temperature storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tetmodis contains
- The active substance is tetrabenazine.
- Each tablet contains 25 mg tetrabenazine.
- The other ingredients are: pregelatinised maize starch, lactose monohydrate, talc, iron oxide yellow E172, magnesium stearate.

What Tetmodis looks like and contents of the pack
Yellow, round, flat tablets with one-side breaking score in white twist-off bottles with 112 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Orpha-Devel Handels und Vertriebs GmbH,
3002 Purkersdorf, Austria

Manufacturer:
Trommsdorff GmbH & Co. KG Arzneimittel, 52477 Alsdorf, Germany

Distributed in the UK and Ireland by
Beacon Pharmaceuticals Ltd.
85, High St., TN1 1YG, UK

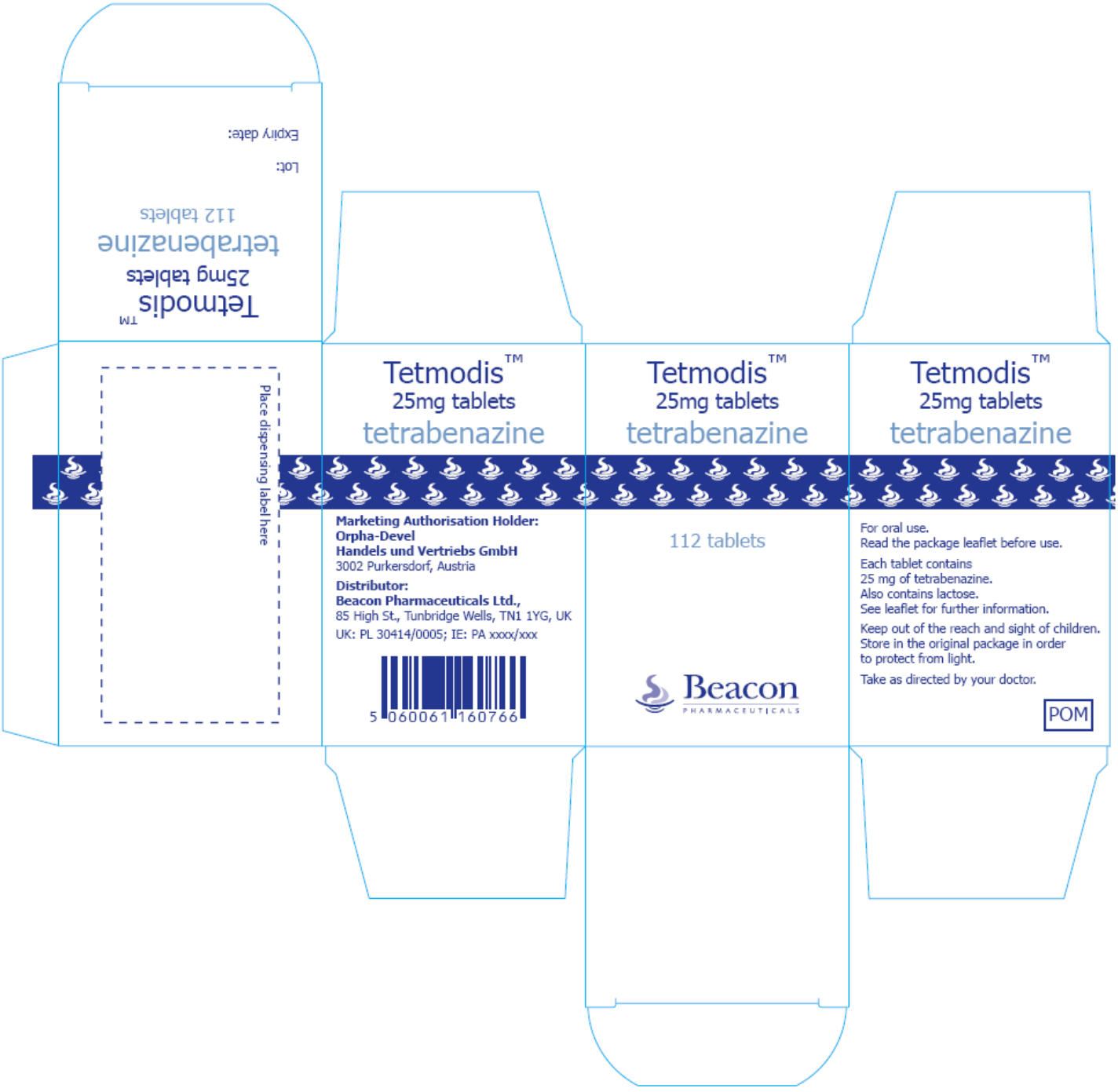
Beacon PHARMACEUTICALS

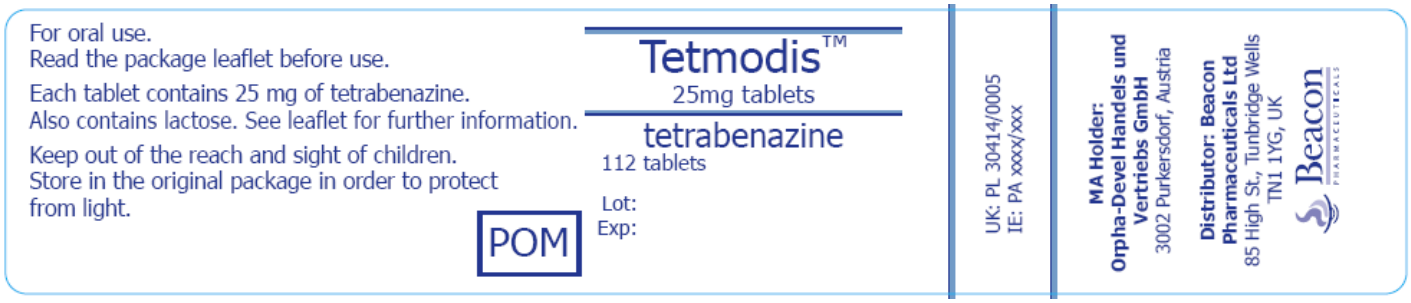
This medicinal product is authorised in the Member States of the EEA under the following names:

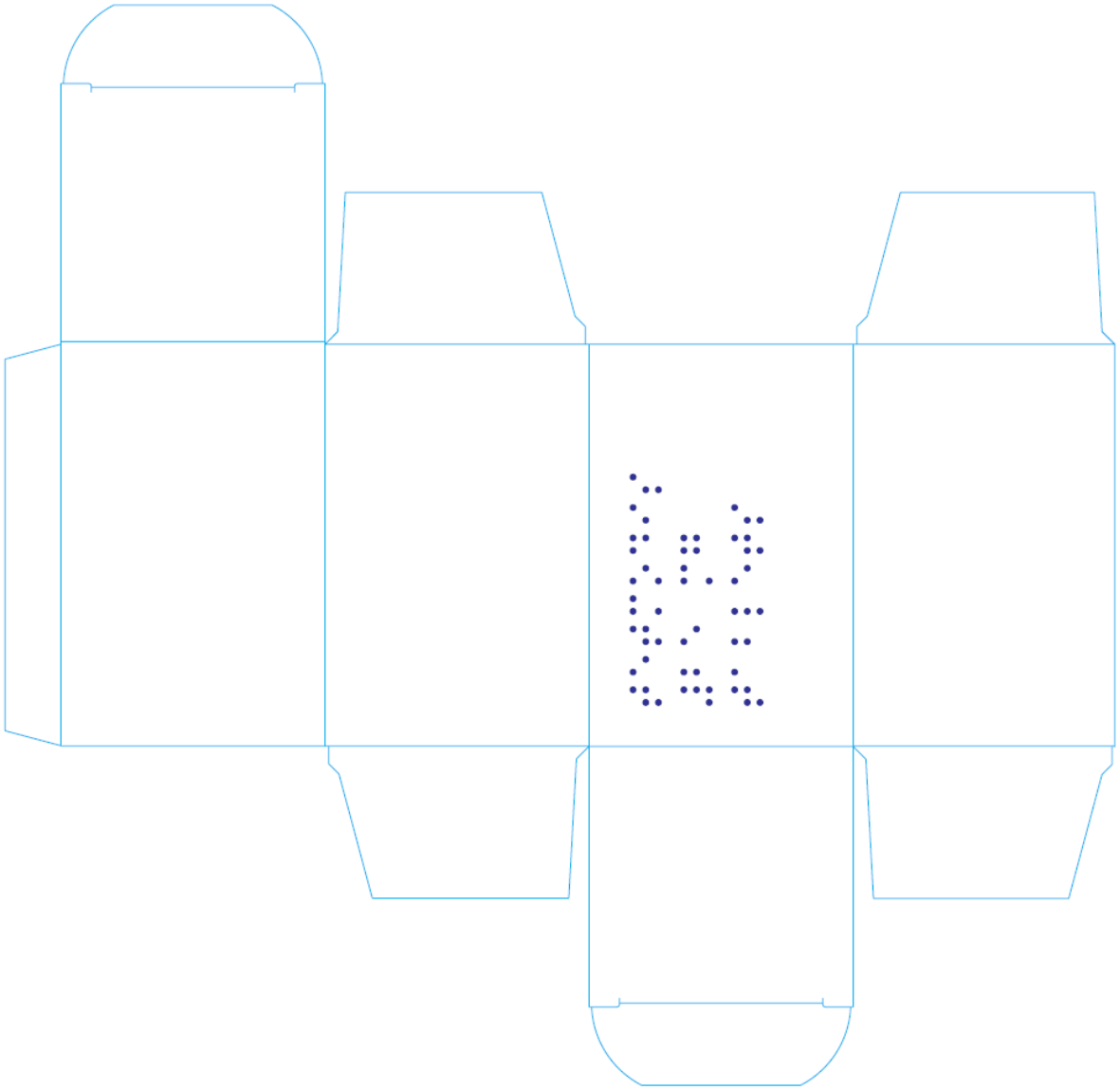
Austria:	Tetmodis 25 mg Tabletten
Belgium:	Tetrabenazine Orpha-Devel Handels und Vertriebs 25 mg tabletten
Bulgaria:	Tetmodis 25 mg таблетки
Czech Republic:	Tetmodis 25 mg tablety
Denmark:	Tetmodis 25 mg tabletter
Estonia:	Tetmodis 25 mg tablett
Finland:	Tetmodis 25 mg taletti
France:	Comprimés Tetmodis 25 mg
Germany:	Tetmodis 25 mg Tabletten
Greece:	Tetmodis 25 mg δισκία
Hungary:	Motetis 25 mg tabletta
Ireland:	Tetmodis 25 mg tablets
Italy:	Tetmodis compresse da 25 mg
Latvia:	Tetmodis 25 mg tabletes
Lithuania:	Tetmodis 25 mg tabletės
Netherlands:	Tetmodis 25 mg tabletten
Poland:	Tetmodis 25 mg tabletki
Portugal:	Comprimidos de Tetmodis 25 mg
Romania:	Tetmodis, tablete, 25 mg
Slovakia:	Tetmodis 25 mg tableta
Slovenia:	Tetmodis 25 mg tablete
Spain:	Tetmodis 25 mg comprimidos
Sweden:	Tetmodis 25 mg tablett
United Kingdom:	Tetmodis 25 mg tablets

This leaflet was last approved in June 2010

Module 4
Labelling







Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria, Belgium, Bulgaria, the Czech Republic, Denmark, Estonia, Germany, Greece, Finland, France, Hungary, Ireland, Italy, Latvia, Lithuania, the Netherlands, Poland, Portugal, Romania, Spain, Slovenia, the Slovak Republic, Sweden and the UK considered that the application for Tetmodis 25mg tablets could be approved. These products are prescription only medicines (POM) indicated for hyperkinetic motor disorders with Huntington's chorea.

This application for Tetmodis 25mg tablets was submitted as an abridged application, according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Xenazine TM/Tetrabenazine 25mg tablets (Lifehealth Limited, UK) which was granted on 23rd October 1995 and cross refers to Nitoman Tablets 25mg (PL 00031/507R) which was granted 20th June 1985 to Roche Products Limited. As Nitoman Tablets 25mg is a full dossier, Xenazine TM/Tetrabenazine 25mg tablets is acceptable as the reference product according to Article 10(2)a.

Tetrabenazine is a novel dopamine depletor that works by selectively blocking the VMAT2 transporter in the central nervous system (CNS) and is indicated for hyperkinetic motor disorders with Huntington's chorea.

Tetrabenazine works mainly as a VMAT inhibitor and, as such, promotes the early metabolic degradation of the neurotransmitter dopamine. It is approved for use in the management of movement disorders and similar symptoms of CNS dysfunction.

No new preclinical studies were conducted, which is acceptable given that the product contains widely-used, well-known active substances. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for this application as the pharmacology of tetrabenazine is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A Risk Management Plan (RMP) has also been submitted and is satisfactory.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Tetmodis 25mg tablets
Name(s) of the active substance(s) (INN)	Tetrabenazine
Pharmacotherapeutic classification (ATC code)	Other nervous system drugs (N07XX06)
Pharmaceutical form and strength(s)	25mg tablets
Reference numbers for the Decentralised Procedure	UK/H/1816/001/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Bulgaria, the Czech Republic, Denmark, Estonia, Germany, Greece, Finland, France, Hungary, Ireland, Italy, Latvia, Lithuania, the Netherlands, Poland, Portugal, Romania, Spain, Slovenia, the Slovak Republic, Sweden
Marketing Authorisation Number(s)	PL 30414/0005
Name and address of the authorisation holder	Orpha-Devel Handels und Vertriebs GmbH, 3002 Purkersdorf, Austria

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

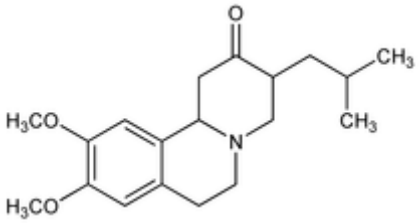
S. Active substance

INN/Ph.Eur name: Tetrabenazine

Chemical name:

- 1,3,4,6,7,11b-Hexahydro-3-isobutyl-9,10-dimethoxybenzo[*a*]quinolizin-2-one (*Martindale*)
- 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2*H*-benzo[*a*]quinolizin-2-one (*Merck Index*)
- 2-oxo-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (*Merck Index*)
- 3-Isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydropyrido[2,1-*a*]isoquinolin-2-one (*LOBA*)

Structural formula:



Molecular formula: $C_{19}H_{27}NO_3$

Appearance: A white or bright yellowish crystalline powder; soluble in ethanol, acetone, chloroform *tert*-butyl-methylether and diethylether; insoluble in water.

Molecular weight: 317.43

Synthesis of the drug substance from the designated starting materials 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.

All potential known impurities have been identified and characterised. Appropriate proof-of-structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

The tablets consists of pharmaceutical excipients pregelatinised maize starch, lactose monohydrate, talc, iron oxide yellow (E172), magnesium stearate.

With the exception of iron oxide yellow (E172), all excipients comply with their respective European Pharmacopoeia monograph. Iron oxide yellow (E172) complies with a suitable in-house specification.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as that intended for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to produce a safe, efficacious product containing tetrabenazine that could be considered a generic medicinal product of Xenazine TM/Tetrabenazine 25mg tablets (Lifehealth Limited, UK) which was granted on 23rd October 1995 and cross refers to Nitoman Tablets 25mg (PL 00031/507R) which was granted 20th June 1985 to Roche Products Limited.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative *in vitro* dissolution profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial-scale batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

These products are packaged in white round high-density polyethylene (HDPE) tablet containers with child-resistant, tamper-evident polypropylene (PP) screw caps and mounted desiccant. The product comes in pack sizes of 112 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product

Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years with special storage instructions, ‘Store in the original package in order to

protect from light'. This medicinal product does not require any special temperature storage conditions.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labelling are pharmaceutically acceptable. Please find the UK PIL and label mock-ups in modules 3 and 4.

User testing results have been submitted for the PIL for these products. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

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

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of tetrabenazine are well-known. As tetrabenazine is widely used, well-known active substance, the applicant has not provided any new pre-clinical data and none are required.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A satisfactory justification has been provided for non-submission of an environmental risk assessment.

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

III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required.

Pharmacokinetics

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover study to compare the pharmacokinetics of the test product Tetrabenazine 25mg tablets versus the reference product Xenazine TM/Tetrabenazine 25mg tablets (Lifehealth Limited, UK) in healthy subjects under fasted conditions.

A dose of the assigned product was administered after a fast of at least 10 hours. Blood samples were taken pre- and up to 72 hours post dose. There was a washout period of 7 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tetrabenazine and its active metabolite α-dihydrotetrabenazine are presented below as log-transformed values:

Treatment	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/ml)
Tetrabenazine:			
Test (T)	1.66	2.11	0.46
Reference (R)	1.44	1.96	0.42
T/R Ratio (90% CI)	1.472 (1.0774 – 1.2216)	1.0905 (1.0192 – 1.1668)	1.0995 (1.0266 – 1.1776)

Treatment	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/ml)
α-dihydrotetrabenazine:			
Test (T)	512.94	519.46	98.31
Reference (R)	455.39	461.62	87.46
T/R Ratio (90% CI)	1.1264 (1.0534 – 1.2044)	1.1253 (1.0533 – 1.2022)	1.1241 (1.0319 – 1.2244)

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for tetrabenazine and its active metabolite, α-dihydrotetrabenazine lie within acceptable limits. Thus, bioequivalence has been shown between the test and reference products in this study.

EFFICACY

No new efficacy data were submitted with this application and none were required.

SAFETY

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM

The MAA Form is medically satisfactory.

CONCLUSIONS

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

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Tetmodis 25mg tablets are 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 an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Tetmodis 25mg tablets and the reference product Xenazine TM/Tetrabenazine 25mg tablets(Lifehealth Limited, UK).

No new or unexpected safety concerns arise from this application.

The SPCs, PIL and labelling are satisfactory and consistent with that for the innovator product.

BENEFIT-RISK ASSESSMENT

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

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome