CBG MEB

Public Assessment Report

Scientific discussion

Tracydal 20 mg, film-coated tablets

(tranylcypromine sulfate)

NL License RVG: 115752

Date: 7 March 2016

This module reflects the scientific discussion for the approval of Tracydal 20 mg, film-coated tablets. The marketing authorisation was granted on 15 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

A list of literature references is given on pages 25-26.

List of abbreviations

AA	Arachidonic Acid
AC	Active Controlled
ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMR	Carcinogenic, Mutagenic, Reprotoxic
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
EDMF	European Drug Master File
ERA	Environmental Risk Assessment
HAM-D	Hamilton Rating Scale for Depression (= HRSD)
HRSD	Hamilton Rating Scale for Depression (= HAM-D)
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MAO	Monoamine Oxidase
MEB	Medicines Evaluation Board of the Netherlands
NICE	National Institute for Health and Care Excellence of the UK
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
PBT	Persistence, Bioaccumulation and Toxicity
PECsw	Predicted Environmental Concentration in surface water
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PUFA	Poly-unsaturated Fatty Acids
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SNRI	Serotonin and Noradrenalin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic antidepressants
TRD	Treatment-resistant Depression
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Tracydal 20 mg film-coated tablets from Daleco Pharma b.v.

Following extensive deliberation of the benefit-risk balance the Board concluded that additional risk minimisation measures are required to warrant safe use of this medicine. Educational material and patient alert cards need to be distributed. Moreover, a registry study should be initiated to monitor the effectiveness of the educational materials. See section IV.5 of this report for further details.

The product is indicated for the treatment of severe, treatment-resistant depressive disorder irresponsive to two preceding, adequate standard anti-depressive treatments (including tricyclic antidepressants) and augmentation with e.g. lithium.

A comprehensive description of the indications and posology is given in the SmPC.

Tranylcypromine is a nonselective and irreversible ('classic') monoamine oxidase (MAO) inhibitor.
The active substance has not been registered in the Netherlands before, but could previously be prescribed with permission from the Health Care Inspectorate, as a 'named patient product', for treatment-resistant depression (TRD). It is registered in the UK as Parnate 10 mg tablets by Mercury Pharmaceuticals Ltd, and in Germany as Jatrosom 20 mg film-coated tablets by Aristo Pharma GmbH. Another not-registered nonselective and irreversible MAO inhibitor that can be prescribed as a named patient product, is phenelzine (Nardil).

The only registered MAO inhibitor for the treatment of depression in the Netherlands is moclobemide (Aurorix, a reversible MAO-A inhibitor). This product was developed specifically to mimic the efficacy of the irreversible MAO inhibitors, without the risk of the 'cheese reaction' associated with the irreversibility of binding to the MAO-enzyme.

Patient exposure to tranylcypromine in the Netherlands can be deduced from data from the Dutch National Health Care Institute (*Zorginstituut Nederland*): on average approximately 1400 patients per year. Patient exposure for phenelzine in the Netherlands is substantially less than to tranylcypromine (data National Health Care Institute: approximately 130 patients per year).

This national procedure concerns a bibliographic application based on the well-established medicinal use of tranylcypromine. No new (pre)clinical studies were conducted. The MAH submitted non-clinical and clinical overviews based on scientific literature.
The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

Scientific advice was given in 2012 with regard to the dossier requirements. A well-established use application was considered possible provided the bibliographic data are of sufficient quality, the current product can be bridged to the product used in these studies, the population of the former studies can be bridged to the current population and the safety can be managed.

II. QUALITY ASPECTS

II.1 Introduction

Tracydal 20 mg is a red, round, convex tablet with a v-shaped break-mark on one side. It contains 27.37 mg of tranylcypromine sulfate corresponding with 20 mg of tranylcypromine. The tablet can be divided into equal doses.

The tablets are packed in a Alu-PVC/PVdC blister strips.

The excipients are:

Tablet core - microcrystalline cellulose (E460), anhydrous calcium hydrogen phosphate (E341), pregelatinised starch, colloidal anhydrous silica (E551), talc (E553B).
Film coating - Opadry II 85F25510, consisting of polyvinyl alcohol-partially hydrolysed (E1203), macrogol 4000, Ponceau 4R Aluminum Lake (E124), talc (E553B), titanium dioxide (E171), and FD&C Blue #2/Indigo Carmine Aluminum Lake (E132).

II.2 Drug Substance

The active substance is tranylcypromine sulfate, an established active substance described in the British Pharmacopoeia (BP). The active substance is soluble in water, very slightly soluble in ethanol (96%) and in ether, and practically insoluble in chloroform. Tranylcypromine sulfate is a racemic mixture. The molecular structure contains 2 asymmetric centres at carbons 1 and 2 of the cyclopropanic ring. The resolution into 2 enantiomers is possible.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The drug substance is manufactured in a three step synthesis followed by a conversion into the appropriate salt (sulfate). Acceptable specifications have been adopted for the starting material, solvents and reagents. All solvents have been adequately limited in the drug substance specification. No catalysts are used.

Quality control of drug substance
The drug substance specification is acceptable in view of the route of synthesis and the various European guidelines. The limits are in accordance with the BP monograph or stricter. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for fourteen commercial-scale batches stored at 25°C/60%RH (up to 60 months) and for 3 batches stored at 40°C/75%RH (6 months). No significant changes were observed during the stability studies. On the basis of the provided stability data the proposed retest period of 60 months without special storage conditions is acceptable.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The presence of a break-mark on the tablet is justified since the starting dose is 10 mg (½ tablet). The functionality has been adequately demonstrated.
The drug product itself shows rapid dissolution throughout the physiological pH range (>95% dissolved in 15 minutes at all 3 pHs tested). The discriminative nature of the routine dissolution method has been adequately demonstrated.
It concerns a well established use application where the drug product was compared with the data described in the literature for two reference products, Parnate (UK) and Jatrosom (Germany). Supportive BCS biowaiver data was included. The two innovator products Parnate and Jatrosom differ in composition and *in vitro* dissolution characteristics. Tracydal has the same indication as these two innovator products and is very rapidly dissolving, thus readily available. From a chemical-pharmaceutical perspective bridging of the published data on the innovator products is adequately justified. The drug product and manufacturing development are adequately described and performed.

Manufacturing process
The manufacturing process is a straightforward process using direct compression. The ingredients are mixed and compressed into tablet cores, and subsequently the cores are film coated. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product has been presented for two commercial-scale batches. A third batch will be validated post approval.

Control of excipients
The excipients comply with the European Pharmacopoeia (Ph.Eur.), and for Opadry an in-house specification is used. These specifications are acceptable. For several excipients additional limits are included with respect to the functionality related parameters as described in the Ph.Eur.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, related substances, disintegration, dissolution, uniformity of dosage units, subdivision of tablets and microbiological quality. The release and shelf-life limits are identical. The analytical methods have been adequately described and validated. The methods for assay and the related substance are stability indicating.
Batch analytical data from the proposed production site have been provided on two commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two commercial-scale batches stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-Al blisters. Under both storage conditions the drug product remains well within the specification for all parameters tested. The drug product was shown to be photostable. On the basis of the available stability data the claimed shelf-life of 24 months is granted, without specific storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Tracydal has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment has been made:

- The MAH will monitor the particle size distribution of the active substance routinely. In case large deviations are observed, dissolution profiles will be recorded and a limit for particle size distribution of the active substance will be reconsidered.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The MAH submitted a non-clinical overview, which is based on a number of review papers, most importantly:

- Baker GB, Coutts RT, McKenna KF, Sherry-McKenna RL (1992). Insight into the mechanisms of action of the MAO inhibitors phenelzine and tranylcypromine: a review.

- Frieling H, Bleich S (2006). Tranylcypromine. New perspectives on an ‘‘old’’ drug.

III.2 Pharmacology

Primary pharmacodynamics

Effects on trace amines and amino acids

The inhibition of MAO by drugs such as phenelzine and tranylcypromine results in an often dramatic elevation of a number of brain amines termed "trace amines" (2-phenylethylamine (PEA), m- and p-tyramine, octopamine, tryptamine) [Philips and Boulton (1979), Boulton and Juorio 1982) in Baker et al (1992)].

The amino acid tryptophan has been used as an adjunct to therapy for affective disorders and in the treatment of refractory depression [Young (1991) in Baker et al (1992)]. Badawy and Evans (1981, 1982) [in Baker et al (1992)] reported that tranylcypromine, as with a number of other antidepressants, inhibited rat liver tryptophan pyrrolase activity and produced elevations of brain tryptophan after both acute and chronic administration of the drugs. Grahame-Smith (1971) [in Baker et al (1992)] and Tabakoff and Moses (1976) [in Baker et al (1992)] also reported an increase in the brain levels of tryptophan in rodents at short intervals after the administration of high doses of tranylcypromine. The findings of Sherry-McKenna et al (1994) indicate that this tryptophan-elevating effect occurs only with high doses of phenelzine and tranylcypromine and is relatively short-lived.

Effects on uptake and release of neurotransmitter amines

The structures of phenelzine and tranylcypromine are similar to those of 2-phenylethylamine (PEA) and amphetamine, and, not surprisingly, they have effects on the uptake and/or release of dopamine, noradrenaline and, to a lesser extent, 5-HT [Hendley and Snyder (1968), Schildkraut (1970), Simpson (1978), Baker et al (1978, 1980), Dyck and Boulton (1980), Reigle et al (1980), Dyck (1984) in Baker et al (1992)].

At the doses of phenelzin and tranylcypromine often used, particularly in studies on laboratory animals, levels of these drugs in the brain that are sufficiently high to affect the uptake and release of these neurotransmitters could be attained [Calverley et al (1981), Dyck 1984) in Baker et al (1992)].
Several reports indicate that high doses of tranylcypromine (1.3 mg to 2.4 mg/kg per day) are effective in treating patients suffering from refractory depression [Robinson (1983), Guze et al (1987), Pearlman (1987), Amsterdam and Berwish (1989) in Baker et al (1992)]. Since these doses are well above those reported to inhibit MAO by more than 90% [Giller and Lieb (1980), Giller et al (1982) in Baker et al (1992)], effects of tranylcypromine other than the inhibition of MAO may contribute to the antidepressant effects of tranylcypromine at the high doses.

Effects on receptors for amines and amino acids

Changes in several pre-synaptic and post-synaptic receptors may occur subsequent to the increased levels of the amines and/or amino acid neurotransmitters. These delayed effects may be associated with the lag between administration of the MAO inhibitors and onset of clinical effect.
Down-regulation of β-adrenoreceptors in rat brain cortex has been reported after the acute and chronic administration of phenelzine and the chronic administration of tranylcypromine [Cohen et al (1982), Frazer and Lucki (1982), Koshikawa et al (1989), McManus and Greenshaw (1991a), Sherry-McKenna et al (1992b) in Baker et al (1992)]. Ordway et al (1991) [in Baker et al (1992)] reported that the chronic administration (21 days) of phenelzine and tranylcypromine (5 mg/kg per day each) to rats produced a down-regulation of both β1- and β2-adrenoceptors in some areas of the brain. Paetsch and Greenshaw (unpublished data, 1992) [in Baker et al (1992)] found that chronic administration (28 days) of tranylcypromine (1 mg/kg per day) or phenelzine (5 mg or 10 mg/kg per day) resulted in β1- but not β2-adrenoceptor down-regulation in the cortex and cerebellum; a similar result was reported by Heal et al (1989) [in Baker et al (1992)] in the cortex using a high dose (10 mg/kg per day) of tranylcypromine, administered for ten days. After chronic administration (21 days), phenelzine, at a dose of 10 mg/kg per day, but not at a lower dose (5 mg/kg per day), attenuated the locomotor suppressant effects of the β-agonist salbutamol (3 mg/kg i.p.) [McManus et al (1991b) in Baker et al (1992)]. Using clonidine as the pharmacological probe, studies on α2- receptor functioning have been conducted on rats and have indicated that tranylcypromine and phenelzine both cause a down-regulation of α2-adrenergic receptors after chronic administration [Greenshaw et al (1988), McKenna et al (1992a) in Baker et al (1992)]. Lloyd et al (1985) [in Baker et al (1992)] reported an up-regulation of $GABA_B$ receptors in the frontal cortex of rats after chronic administration of the MAO inhibitor

pargyline, but McManus and Greenshaw (1991a,b) [in Baker et al (1992)] reported that phenelzine did not affect $GABA_B$ receptor density or functioning, as measured in neurochemical and behavioral experiments, respectively. Chronic administration of tranylcypromine leads to a selectively increased expression of the $GABA_{B(1a)}$ subunit of the receptor in rats hippocampus. Only tranylcypromine leads also to an increase of the expression of $GABA_{B(2)}$ subunit. Treatment of rats with tranylcypromine significantly enhanced the response to baclofen, a $GABA_B$-receptor agonist, in the hippocampal tissue and leads to an increase of locomotor activity after amphetamine administration [Sands et al (2003), Sands et al (2004) in Frieling et al (2006)].
The chronic administration of both phenelzine and tranylcypromine has been reported to cause a decrease in the density of 3H-tryptamine binding sites in the brains of rats [Mousseau et al (1994) in Baker et al (1992)]. Binding studies have demonstrated a downregulation of 5-HT2 [Goodnough et al (1992) in Baker et al (1992)] receptors in rats' brains after the chronic administration of tranylcypromien. Based on comprehensive electrophysiological studies Blier et al (1990) [in Baker et al (1992)], concluded that MAO inhibitors (including phenelzine) may act in the CNS by increasing the efficacy of 5-HT neurons through down-regulation of the somatodendritic autoreceptor. Paetsch and Greenshaw (1992) [in Baker et al (1992)] found that the chronic administration of phenelzine or tranylcypromine results in the downregulation of both D1 and D2 dopamine receptors in the striatum of rats. Chronic administration of some antidepressants has been reported to result in the down-regulation of 3H-flunitrazepam receptors in rats' brains [Suranyi-Cadotte et al (1984) in Baker et al (1992)] (MAO inhibitors were not tested).
The chronic administration of tranylcypromine or phenelzine, at relatively low doses sufficient to down-regulate β-adrenergic and tryptamine receptors, has been found to produce no down-regulation of 3H-flunitrazepam receptors in the cortex of rats [McKenna et al 1992b, Todd et al 1992) in Baker et al (1992)]; similar negative results were obtained with tranylcypromine (at an i.p. dose of 5 mg/kg b.i.d. for 21 days) by Kimber et al (1987) [in Baker et al (1992)].
Experiments were aimed at comparing the effects of high doses (2.5 mg/kg/day) and low doses (0.5 mg/kg/day) of tranylcypromine on tryptamine and 5-HT2 receptors in the cortex of rats. The findings can be summarized as follows: 1. both high and low doses of tranylcypromine produce a decrease in the number of tryptamine receptors in cortex [Goodnough et al 1992, Sherry-McKenna et al 1992a) in Baker et al (1992)], but the effect is more rapid with the high dose [Goodnough et al (1992) in Baker et al (1992)]; and 2. a high dose of tranylcypromine produces a greater decrease in 5-HT2 receptor number in the cortex than the low dose [Goodnough and Baker (1992) in Baker et al (1992)].

Effects on enzymes other than MAO
Robinson et al (1979) [in Baker et al (1992)] reported that chronic administration of tranylcypromine is associated with an increase in activity of aromatic amino acid decarboxylase. This observation may be related to the finding that chronic administration (up to 18 days) of tranylcypromine (10 mg/k.g i.p. daily) to rats produced a much greater elevation of brain tryptamine than did phenelzine (15 mg/k.g i.p. daily) at the same time periods, despite the fact that both drugs inhibited MAO by more than 90% by day 2 [Baker et al (1984) in Baker et al (1992)].

Activity of metabolites
Preliminary experiments by Baker et al (1992) have shown that 4-hydroxy-tranylcypromine is an inhibitor of MAO-A and MAO-B, but is weaker than the parent drug in this regard. It is known that tranylcypromine itself has such actions [Baker et al (1978, 1980), Hendley and Snyder (1968), Horn and Snyder (1972), Schildkraut (1970) in Baker et al (1992)]. The addition of a 4-hydroxy group on the structurally related amine 2-phenylethylamine (PEA) has been reported to enhance its effect on biogenic amine transport in synaptosomes [Raiteri et al (1977) in Baker et al 1992)].

Secondary Pharmacodynamics
Effects on phospholipids and lipid-mediators
Abnormalities in the metabolism of phospholipids have been implicated in the pathophysiology of depressive disorders. Phospholipids are essential for neuronal and synaptic structures and play key roles in the signal transduction response to different neurotransmitters [Bazan (2003) in Frieling et al (2006)]. Phospholipid derived mediators like prostaglandins, leukotrienes and thromboxanes are fundamental for many functions of the organism, e.g. the immune system. Especially, the role of poly-unsaturated fatty acids (PUFA) like omega-3 (ω3) or omega-6 (ω6) fatty acids and the ω3/ω6-ratio in the plasma membrane and lipid mediators has been widely investigated [Haag (2003) in Frieling et al (2006)]. In depressed patients, an imbalance in PUFAs has been found with an excess of ω6 acids like arachidonic acid (AA) and a deficiency of ω3 fatty acids, such as eicosapentaenoic or

docosahexaenoic acid. It was postulated that overactivity of different enzymes of the arachidonic cascade, like phospholipase A2 (PLA2) or coenzyme-A-independent transaminase (CoAIT) was underlying this imbalance, as diet did not seem to be its main cause [Horrobin (2001) in Frieling et al (2006)]. CoAIT is of special interest, as this enzyme specifically affects only AA but not ω3-fatty acids [Winkler et al (1995) in Frieling et al (2006)]. Tranylcypromine is known to inhibit the release of AA from bradykinin-stimulated endothelial cells. It remains unclear, if this effect is due to PLA inhibition or if another enzyme is involved. It could be hypothesized that tranylcypromine inhibits CoAIT and therefore attenuates the ω3/ω6 imbalance by reducing the AA release. It is well known that lipid mediators derived from ω3 fatty acids are more potent anti-inflammatory and less potent proinflammatory agents than those derived from ω6 fatty acids and may therefore excert positive effects on immune disturbances observed during depression [Simopoulos (2002) in Frieling et al (2006)]. Other effective anti-depressive therapies like electroconvulsive therapy or lithium salts also affect the arachidonic cascade making the modulation of phospholipids an interesting target for novel antidepressants [Altar et al (2004), Rapoport et al (2002) in Frieling et al (2006)].
Tranylcypromine does not only affect AA release but also inhibits the prostacyclin synthase and therefore decreases the prostacyclin (PGI2) production [Hong et al (1980) in Frieling et al (2006)]. Until recently, this property of tranylcypromine has not found attention in psychiatric research. PGI2 is one of the prominent endothelium derived vasodilating mediators [Gordon et al (1979), Parkington et al (2004) in Frieling et al (2006)]. It is, therefore, surprising that tranylcypromine neither has vasorelaxing nor vasoconstricting properties *in vitro*, unlike other antidepressants (i.e. amitriptyline) that lead to full relaxation of smooth muscles *in vitro*. This finding is of special interest, as both agents lead to orthostatic hypotension as one of their main side-effects. In the case of tranylcypromine, it is unlikely to be mediated by peripheral effects of the drug, even though tranylcypromine interacts with different vasomotor controlling pathways.

Safety pharmacology
Levels of free tranylcypromine may contribute to the side-effects of this drug. In a study examining depressed patients, a correlation was found between mean plasma concentrations of tranylcypromine and mean orthostatic drop of systolic blood pressure and a rise in pulse rate [Mallinger et al (1986) in Baker et al (1992)]. Keck et al (1991) [in Baker et al (1992)] found that elevations in blood pressure were significantly correlated with the dose of tranylcypromine; they hypothesized that the initial hypertensive response to tranylcypromine is mediated by noradrenaline and that the orthostatic hypotensive effect is mediated by a direct interaction between tranylcypromine and a-adrenergic receptors.

No information on CNS or respiratory safety pharmacology has been provided.

Pharmacodynamic drug interactions
The concomitant use of tranylcypromine and other drugs is restricted not only because of the elevated risk for hypertensive crisis or central serotonergic syndrome but also because of some possible interactions concerning cytochrome P-450 based drug degradation.

III.3 Pharmacokinetics

Metabolism
Alleva (1965) [in Baker et al (1992)] reported hippuric acid as a metabolite of tranylcypromine, but concluded that amphetamine was not involved as an intermediate in this metabolism. The metabolic formation of amphetamine from tranylcypromine continues to be debated. Youdim et al (1979) [in Baker et al (1992)] reported the presence of amphetamine in the plasma of a patient who had overdosed on tranylcypromine, but studies conducted by Reynolds et al (1980) on humans and by Sherry-McKenna et al (1992a) [in Baker et al (1992)] on humans and rats have not revealed amphetamine in human urine or rat brain after the administration of pharmacologically relevant doses of tranylcypromine. The presence of the N-acetyl [Calverley et al (1981) in Baker et al 1992)] and ring hydroxylated [Baker et Al (1986), Nazarali et al (1987) in Baker et al 1992)] metabolites of tranylcypromine have been demonstrated in rats' brains. Kang and Chung (1984) [in Baker etal 1992)] confirmed the formation of N-acetyltranylcypromine and also identified N-acetyl-4-hydroxy-tranylcypromine as a tranylcypromine metabolite in rats' urine.

Pharmacokinetic drug interactions

There are also reports of phenelzine and tranylcypromine interacting with enzymes involved in drug metabolism [Gaultieri and Powell (1978), Tollefson (1983), McDaniel (1986) in Baker et al (1992)]. Patients who are prescribed phenelzine or tranylcypromine may be taking other drugs concomitantly and thus metabolic drug-drug interactions may occur. MAO inhibitors have been reported to inhibit the degradation of such drugs as hexobarbital, ethylmorphine, aminopyrine, meperidine and antipyrine [Eade and Renton (1970), Clark et al (1972), Smith et al (1980), McDaniel (1986) in Baker et al (1992)]. Belanger and Atitse-Gbeasson (1982a, 1982b) [in Baker et al (1992)] found that phenelzine and tranylcypromine inhibited demethylation of p-nitroanisole and N,Ndimethylaniline and hydroxylation of aniline in rat liver microsomes. They concluded that both drugs are inhibitors of oxidative microsomal reactions through an interaction with cytochrome P-450. Dupont et al (1987) [in Baker et al (1992)] studied the effects of MAO inhibitors on cytochrome P-450-dependent hydroxylation of bufuralol and antipyrine and 0-deethylation of 7-ethoxycoumarin in rat liver microsomes. Although phenelzine and tranylcypromine were both able to inhibit hydroxylation of antipyrine, phenelzine caused a much more potent inhibition of bufuralol hydroxylation and 7-ethoxycoumarin 0-deethylation than tranylcypromine.

Tranylcypromine is a potent inhibitor of CYP2A6 [Draper et al (1997) in Frieling et al (2006)], CYP2E1 and, to a lesser extent, CYP1A2, CYP2C9, CYP2C19, CYP3A4 and CYP2D6. The effectivity of CYP inhibition depends on the amino group of tranylcypromine. The non-amine homologue of tranylcypromine, cyclopropylbenzene, is a much less potent inhibitor of CYP1A2, CYP2A6, CYP2C19 and CYP2E1 activities and did not inhibit CYP2C9, CYP2D6 and CYP3A4 [Taavitsainen et al (2001) in Frieling et al (2006)]. However, the inhibitory effects of tranylcypromine on the ‘‘usual suspects’’ for CYP-based drug–drug interaction, CYP2C9, CYP2C19 and CYP3A4 are not considered clinically relevant. During high-dose tranylcypromine therapy or in poor metabolizers of CYP2C19 substrates, clinically relevant interaction may occur [Salsali et al (2004) in Frieling et al (2006)]. CYP2A6 is the principle enzyme metabolizing nicotine to its inactive metabolite cotinine.

The pharmacokinetic information provided is limited to a discussion on metabolism and pharmacokinetic drug-drug interaction. Other relevant information such as protein binding, transport inhibition is lacking.

III.4 Toxicology

The provided information on genotoxicity is limited. The assay for DNA damage by antidepressants in C6 glioma cells published by Slamon et al (2001) is a non-standard assay and difficult to interpret. However, in the study published by Balbi et al (1980), 4 different strains of S. typhimurium were tested with and without S9 mix for metabolic activation and positive controls were included in each assay. Therefore, it can be concluded with reasonable certainty that there is no actual concern for genotoxicity posed by the active substance.

The available reproductive toxicity data have been summarised by the MAH. Although data are very limited, there are some signals of teratogenic potential. However, the data are too limited to conclude on the reproductive toxicity potential. This is reflected in the SmPC.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

The MAH provided the results of an Environmental Risk Assessment.

Summary of main study results

Substance (INN/Invented Name): tranylcypromine			
CAS-number (if available): 155-09-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	shake flask	log K_{ow} = 1.58 at pH 13	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log K_{ow} = 1.58 at pH 13	not B
	BCF	not triggered	

Persistence	ready biodegradability	PM	P/not P
	DT50	PM	P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement	Tranylcypromine is considered not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default F_{pen}	0.3	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	not investigated		

It has been sufficiently demonstrated that the log Kow of tranylcypromine is below the trigger value of 3. The log K_{ow} value of 1.58 (at pH 13) is accepted.
The MAH proposed a refined F_{pen} based on sales data. The MEB considers that prevalence data should be used that are well underpinned. However, tranylcypromine is a last resort medicine, only used in few patients. The estimate of 1500 patient years for the Netherlands is considered a realistic estimate. Therefore, it is accepted that it is very unlikely that the trigger value for a Phase II assessment will be exceeded and no further data are required for the environmental risk assessment for marketing authorisation of tranylcypromine for the proposed indication. If an increase of environmental exposure occurs post approval, where PEC_{sw} exceeds the action limit of 0.01 µg/L, a Phase II assessment is warranted.

III.6 Discussion on the non-clinical aspects

Tranylcypromine is a well established active substance which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on scientific literature. The overview justifies that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application for Tracydal is based on the well-established use of tranylcypromine in the Netherlands and a number of other European countries. It is recommended in Dutch and international treatment guidelines (NICE, US) as third or fourth line treatment option in treatment-resistant patients with severe depression, not responding to at least two other treatments.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data.

It is estimated that 17–21% of patients suffering from major depression have a poor outcome after 2 years, and 8–13% have a poor outcome even after 5 years of treatment [Winokur et al (1993) in Schlaepfer et al (2012)]. The STAR*D study (n=3671) showed that remission rates (QIDS-SR16 score ≤5) are approximately 37% after first-line treatment with citalopram, decreasing to 31% for second-line treatment, 14% for third-line treatment and 13% for fourth-line treatment options [Warden et al (2007) in Schlaepfer et al (2012)]. This leaves a group of non-responders often generally referred to as ‘treatment resistant’. In the Dutch clinical treatment guideline SSRIs or SNRIs are recommended as first line treatment options, followed by ‘classical’ tricyclic antidepressants as second line, addition of lithium as a third option, and MAO inhibitors as a fourth option, to be followed only by electroconvulsive therapy (ECT).

IV.2 Pharmacodynamics/pharmacokinetics

MAO is a flavin-containing enzyme critical for the regulation of the activity of several neurotransmitters. It catabolizes endogenous monoamines (e.g. norepinephrine, serotonin, and dopamine) and

exogenous amines (e.g. dietary tyramine). It is present throughout the body but in higher concentrations in the liver, kidneys, intestinal wall, and brain.
MAO has two distinctly distributed subtypes, isoenzyme A (MAO-A) and isoenzyme B (MAO-B). MAO-A is found primarily in the intestinal tract, liver, and peripheral adrenergic neurons (adrenal glands, arterial vessels, and sympathetic nerves) and preferentially metabolizes serotonin and norepinephrine, MAO-B is found mostly in the brain and liver. Since 80% of intestinal MAO is MAO-A, this isoenzyme is primarily involved in the degradation of tyramine, and thus inhibition of MAO-A is associated with the so called 'cheese reaction', i.e. a hypertensive crisis after taking tyramine-rich food or drinks, such as ripened cheese or red wine (Horwitz et al., 1964; Asatoor et al., 1963).

Several studies were cited in the pharmacokinetic overview. The following four studies were submitted:

- Frieling H, Bleich S (2006). Tranylcypromine. New perspectives on an ''old'' drug.
- Gillman PK (2011). Advances pertaining to the pharmacology and interactions of irreversible nonselective monoamine oxidase inhibitors.
- Mallinger AG, Edwards DJ, Himmelhoch JM, Knopf S, Ehler J (1986). Pharmacokinetics of tranylcypromine in patients who are depressed: relationship to cardiovascular effects
- Ostad Haji E, Hiemke C, Pfuhlmann B (2012). Therapeutic drug monitoring for antidepressant drug treatment.

Of the 4 studies submitted, only the study of Mallinger et al (1986) provides concrete data for the pharmacokinetics of tranylcypromine. The other 3 were reviews of published studies on tranylcypromine. Hence only the study of Mallinger et al is discussed.
The study was performed in 9 patients with depression who had been treated for at least 1 month with tranylcypromine in a dose range of 20 and 50 mg/day. On the night of the study subjects fasted. Baseline samples were taken 18 hours after the most recent tranylcypromine dose, ranged from 0 to 3 ng/ml. A total dose of 20 mg of tranylcypromine (two 10 mg tablets of a standard formulation Parnate) was then given orally. Blood samples were then taken at different time points until 10 hours post dose.

A summary of the results is provided below.

Subject characteristics and kinetics of tranylcypromine after 20 mg oral dose.

	Observed range or ratio	*Mean ± SD (n = 9)*
Subject characteristics		
Age (yr)	24-49	35.4 ± 7.1
Weight (kg)	50.8-99.3	70.1 ± 15.5
Sex (M/F)	2/7	
Cigarette smoker (yes/no)	3/6	
Tranylcypromine kinetics		
Observed peak plasma concentration (ng/ml)	64.5-190	112 ± 41
Time of peak plasma concentration (hr)	0.67-3.50	1.55 ± 0.99
Measured AUC (ng/ml × hr)	145-568	373 ± 125
Total AUC (ng/ml × hr)	151-645	430 ± 140
k_e (hr^{-1})	0.220-0.451	0.301 ± 0.086
Elimination $t_{1/2}$ (hr)	1.54-3.15	2.45 ± 0.57
Volume of distribution (L/kg)	1.11-5.68	2.71 ± 1.29
Clearance (ml/min/kg)	6.40-40.6	14.1 ± 10.3

In the proposed SmPC for Tracydal, the pharmacokinetics characteristics are based on the data of Mallinger et al. (1986), and the same as the characteristics stated in the SmPC of the German product Jatrosom.

The information on the pharmacokinetic interactions is derived from the review paper of Gillman (2011). Additional information was derived from the study of Balon et al (1990) and Murphy et al (1986). The Netherlands Pharmacovigilance Centre Lareb received two reports about patients who developed a serotonin syndrome after the combined use of trazodone and tranylcypromine. The probable interaction mechanism is an additive serotonergic effect. In addition there is a lot of information on the interaction of tranylcypromine with other drugs in available public drug-drug interaction (DDI) databases.

Biowaiver

No bioequivalence studies have been conducted with Tracydal. The excipients are widely used in the manufacturing of oral pharmaceutical products and no influence of the excipients on the absorption of tranylcypromine has been reported.

A Biopharmaceutics Classification System (BCS)-based biowaiver was applied for, which is considered supportive for this well-established use application. Based on the available information in the literature on its permeability and solubility data (in water), the MAH considers that the tranylcypromine can be classified as a BCS-class 3 drug. However, no solubility data at pH 1.2, 4.5 and 6.8 were provided. Hence, a conclusion on the BCS classification cannot be drawn.

Dissolution of the test product and the innovator product Jatrosom were shown to be similar as both dissolved more than 85% within 15 minutes at the required pH 1.2, 4.5 and 6.8. The test product and innovator product Parnate were shown to be more or less comparable at pH 1.2 but not at pH 4.5 and 6.8. The difference in the dissolution profiles was attributed to a lag-time of 10-15 minutes for Parnate due to its sugar coating. This explanation is plausible.

Based on the available literature data of the 2 innovator products, it appears that the *in-vitro* drug release does not significantly impact on the *in-vivo* behavior, efficacy and safety of tranylcypromine.

This is in line with the mechanism of action of tranylcypromine: irreversible blockage of the monoamine oxidase enzyme. The duration of action is, therefore, not determined by elimination of the drug but by the rate at which *de novo* synthesis of monoamine oxidase occurs.

Overall, the 2 innovator products differ in composition but both are (almost) exclusively used for the treatment of treatment-resistant depression (TRD). This suggests that the difference in excipients and dissolution is not relevant. Considering that about 50% of the literature are from the 2 innovator products, the proposed product is also intended for the treatment of TRD as these two innovator products and is very rapidly dissolving, so readily available, the literature and data submitted are considered sufficient to bridge the proposed product to the products described in the literature.

IV.3 Clinical efficacy

First presented are the trials that included patients who fall under the definition of TRD as defined in the current CPMP guideline: "treatment-resistant depression is considered, when treatment with at least two different antidepressant agents (of the same or a different class) prescribed in adequate dosages for adequate duration and adequate affirmation of treatment adherence showed lack of clinically meaningful improvement".

Studies that have included patients who did not meet the aforementioned definition in the CPMP guideline are presented separately. These studies are considered to be supportive for the efficacy of tranylcypromine in patients who at least failed one prior antidepressant agent.

- Clinical trials in TRD patients who at least failed two different antidepressant agents

There are 6 studies published using tranylcypromine in TRD patients who had not responded to at least 2 treatments of adequate dose and duration with two different antidepressant. These studies are shown in Table 1. They are listed in chronological order and only the efficacy results of these trials are described.

Table 1. Clinical trials in TRD patients who at least failed two different antidepressant agents

Trial (reference)	Study type	Criteria	Resistant to prior medication	Tranyl-cypromine Mean daily dose (range)	Definition of response to treatment	Response rates tranylcypromine	Comparator	Response rates comparators
Nolen et al (1988) Study 1 First treatment period	AC open partial cross-over	DSM-III	TCA and SSRI or SNRI and Sleep deprivation	80.7 mg/day (range 60-100)	a reduction of at least 50% on the HRSD	8/14 (57%) 6/14 (43%) effect at least 6 months	L-5HTP	0/12 (0%)
Second treatment period/cross over phase				78 mg/day (range 40-100)	a reduction of at least 50% on the HRSD	8/12 (67%), 8/12 (67%) effect at least 6 months		0/5 (0%)
Study 2 First treatment period	AC double-blind cross-over	DSM-III	TCA and SSRI or SNRI and Sleep deprivation	78 mg/day (range 40-100)	a reduction of at least 50% on the HRSD	5/11 (45%) 4/11 (36%) effect at least 6 months	Nomifensine	1/10 (10%) 0/10 (0%) effect lasted at least 6 months
Second treatment period/cross over phase				71 mg/day (range 20-100)	a reduction of at least 50% on the HRSD	5/8 (62%) 4/8 (50%) effect at least 6 months		0/5 (0%)
Grand total						26/45 (58%) 22/45 (49%) effect at least 6 months		
Amsterdam (1991)	Uncontrolled, open label	DSM-III	≥ two prior antidepressants	128 mg/day (range not provided)	complete response (CR)= a reduction of at least 50% on the HRSD + final HRSD≤ 10 partial response (PR)= a reduction of at least 30% on the HRSD + final HRSD> 10	7/14 (50%) CR 3/14 (21%) PR		
Volz et al (1994b)	AC double-blind	DSM-III	≥ two classes of antidepressants	Not provided (range 20-30)	a reduction of at least 50% on the HRSD	34/47 (72.3%)	Brofaromine	34/46 (73.9%)
McGrath et al (2006)	AC open-label	DSM-IV	citalopram and at least two subsequent medication treatments including augmentation treatments	36.9 mg/day (range not provided)	a final HRSD ≤7 (called: remission)	4/58 (6.9%)	Venlafaxine plus mirtazapine	7/51 (13.7%)
Stewart et al (2014)	Uncontrolled, open label	DSM-IV	≥two standard antidepressant medications having different mechanisms	Step 1: 56 mg/day (range 10-60) Step 2:105 mg/day (range 60-120)	an HRSD-21 ≤ 7 maintained for 4 weeks (called remission)	Step 1:7/27 (26%) Step 2:6/20 (30%) Overall: 13 (46%)		

Nolen et al reported on two studies performed to investigate the efficacy of tranylcypromine in TRD patients [**Nolen** et al (1988)]. Both studies were the follow-up study of two earlier double-blind, crossover studies, involving a total of 89 patients, on the effects of oxaprotiline and fluvoxamine in non-responders to TCA treatment. Patients suffering from major depression according to DSM-III criteria with an entry score of at least 18 points of the Hamilton Rating Scale for Depression (HRSD (if number of items is not specified it refers to the 17-item HRSD)), aged between 20-65 years, were included. Seventy-one of them were non-responders to earlier treatments with cyclic antidepressants before treatment with oxaprotiline or fluvoxamine. Of the original group of 89 patients, only those patients who had not responded to either oxaprotiline or fluvoxamine (both given during four weeks in a maximal daily dose of 300 mg) were eligible for the studies presented here and can be considered resistant to TCA and SNRI/SSRI. The patients included had also been unsuccessfully treated with sleep deprivation (four times during two weeks).

Study design of the first study was an open label, partial cross-over design, i.e. only non-responders to the first treatment period of four weeks were, after a subsequent washout period of one week, treated with the opposite drug. Response to treatment was defined as a reduction of at least 50% on the HRSD in comparison to the entry score before the first treatment of the preceding study (oxaprotiline or fluvoxamine). Tranylcypromine was compared to L-5-hydroxytryptophan (L-5HTP) and both medications were started at a lower dose and doses were increased at pre-defined time points in case of insufficient response. Twenty-six patients were included and in the first treatment period 14 patients received tranylcypromine and 12 patients received L-5HTP. Six (43%) of the patients receiving tranylcypromine had response that lasted for at least 6 months and another two had a response but relapsed within 6 months (mean dose 80.7 mg/day; range 60-100 mg), while no patient responded to L-5HTP (mean dose 191.7 mg/day; range 100-200 mg). The patients that did not respond to treatment were crossed-over to the other treatment, i.e. the 12 patients that did not respond to L-5HTP were now treated with tranylcypromine and five of the six (one refused treatment with L-5HTP) that had been unsuccessfully treated with tranylcypromine were now treated with L-5HTP. Again, no positive effect was seen in the group treated with L-5HTP (mean dose 180 mg/day; range 100-200 mg), while eight (67%) patients treated with tranylcypromine (mean dose 78 mg/day; range 40-100 mg) showed a response lasting for at least 6 months.

When interim analysis of the first study revealed the ineffectiveness of L-5HTP, the investigators decided to compare tranylcypromine double-blindly with nomifensine in a second study. In this second study, tranylcypromine was compared to nomifensine, and similar method of increasing doses was used as in the first study. In the first treatment period of this study, five of the 11 patients treated with tranylcypromine (45%) responded (mean dose 78 mg/day; range 40-100 mg); in 4 of them (36%) this effect lasted for at least 6 months. In contrast, nomifensine (mean dose 235 mg/day; range 150-250 mg) was effective, but only temporarily (i.e. for less than 6 months), in 1 out of 10 patients (10%). Although the differences in the numbers of responders are not significant, statistical analysis of the percentage changes in HRSD scores did result in significant differences in favor of tranylcypromine at the end of the last 3 weeks of treatment. In the second treatment period (i.e. cross over phase) eight patients were given tranylcypromine (mean dose 71 mg/day; range 20-100 mg) and five nomifensine (mean dose 250 mg/day, no range given). Five of the eight patients (62%) responded to tranylcypromine, but one relapsed within six months. Treatment with nomifensine did not result in a positive effect in any of the patients.

The overall results of the two studies is that of the 45 patients who were treated with tranylcypromine, 26 (58%) responded within 4 weeks while these results lasted for at least 6 months for 22 (49%). Additionally, after termination of the study, another 5 patients, who had not responded to either oxaprotiline or fluvoxamine in the preceding studies, were treated openly with tranylcypromine. Three of them also responded, resulting in a total of 29 responders out of 50 TRD patients receiving tranylcypromine.

Amsterdam (1991) performed an open-label study in 14 patients with high doses of tranylcypromine, ranging from 90 mg to 180 mg daily, in depressed patients refractory to at least two prior antidepressant treatments (results of first 7 patients were also reported in **Amsterdam and Berwish** (1989)). All subjects satisfied DSM-III criteria for major depressive disorder, single or recurrent episode. All subjects had a minimum HRSD score of at least 20 on a 21-item scale, and all had a clear history of nonresponse to at least two prior medication treatments during the current episode. Initial dosing began at 20 mg daily, with 10 mg increments given at intervals of every third day to weekly. The minimum and maximum tranylcypromine doses were set at 90 mg and 170 mg, respectively, and all patients received doses ≥ 90 mg for a minimum of 3 weeks. Complete response to treatment was

defined as a 50% reduction in the baseline HRSD score plus a final value of no more than 10, while partial response was defined as a at least 30% reduction plus a final HRSD score of more than 10.
Overall, HRSD scores decreased from 24 ± 5 (range 20-37) to 10 ± 8 (range 4-30) at a mean (± SD) daily tranylcypromine dose of 128 ± 27 mg. For responders the mean (± SD) daily tranylcypromine dose was: 113 ± 14 mg. Seven of 14 subjects (50%) who were previously resistant to an average of nine prior treatments had a complete response, and three patients (21%) had a partial response to treatment.

Volz et al (1994b) performed a 6-week, double-blind, multicentre comparison of brofaromine and tranylcypromine. Brofaromine was given at a dose of 100 mg/day and tranylcypromine was administered at a dose of 20 mg/day. If the therapeutic effect was not sufficient after 2 weeks (HRSD reduction by less than 50%), the doses of the test drugs could be increased to 150 mg/day or 30 mg/day, respectively. The patients included showed an unsatisfactory response to a course of treatment with at least two classes of antidepressants (excluding MAO inhibitors) administered in an adequate dose for at least 3 weeks each and had to have a score of at least 18 on the HRSD-21. Response was defined as a 50% reduction on the HRSD after 6 weeks treatment.
In each group 34 patients responded to treatment leading to a 72.34% response in the tranylcypromine group and 73.91% response in the brofaromine group. Other efficacy parameters also demonstrated that there was no difference between the two groups.

McGrath et al. (2006) reported the results of tranylcypromine versus a combination treatment with extended-release venlafaxine and mirtazapine in patients with highly treatment-resistant major depression whose current depressive episode had not responded adequately to treatment in three prior prospective medication trials, as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (level 4 results).

*Short description of the STAR*D study design:*
In level 1, all participants received citalopram. In level 2, participants could be assigned to treatment switch, in which case citalopram was stopped and participants could receive sustained-release bupropion, sertraline, extended-release venlafaxine, or cognitive therapy, or they could be assigned to one of three augmentation treatments, in which case citalopram was continued and sustained-release bupropion, buspirone, or cognitive therapy was added. In level 2A, which was available only to level 2 participants who had received either cognitive therapy alone or cognitive therapy plus citalopram, participants switched either to sustained-release bupropion or to extended-release venlafaxine. In level 3, participants either switched to nortriptyline or mirtazapine or received augmentation treatment with lithium or triiodothyronine (T3). Participants who did not achieve remission with, or were intolerant of, citalopram and at least two subsequent medication treatments went on to level 4, in which they underwent randomized assignment to treatment with either tranylcypromine or a combination of extended-release venlafaxine and mirtazapine.

Fifty-eight patients were randomized to receive tranylcypromine (mean dose 36.9 mg/day, SD = 18.5) and 51 patients to the combination therapy (venlafaxine, 210.3 mg, SD=95.2 and mirtazapine, 35.7 mg, SD=17.6). Remission rates (defined as a score ≤ 7 at exit on the 17-item HRSD) were low in both treatment arms, and the rates were not statistically significantly different between the two treatment groups (6.9% for the tranylcypromine group and 13.7% for the venlafaxine plus mirtazapine group).

Stewart et al (2014) treated patients, who had not responded to high dose treatment of at least two antidepressants for at least 4 weeks, with open label tranylcypromine. All patients met the DSM-IV criteria for major depressive disorder unresponsive to adequate treatment with two or more standard antidepressant medications having different mechanisms. The treatment was introduced in five sequential steps. Shift to the next step occurred only after non-remission was documented following four weeks on maximal prior step dose. Step 1 was the usual dose of tranylcypromine (to 60 mg/day). Step 2 was treatment with high dose tranylcypromine (to 120 mg/day) and step 3 was treatment with tranylcypromine plus dextroamphetamine (unless dextroamphetamine was contraindicated or refused by the patient). Step 4 was treatment with nortriptyline plus lithium, both titrated to standard blood levels. Patients that had not responded to step 3 (or step 2, if step 3 was not possible) tapered tranylcypromine (and dextroamphetamine), and after a two-week delay step 4 was started. Inefficacy during Step 4 led to the addition of phenelzine (step 5). Remission was defined as HRSD-21 ≤ 7 maintained for four weeks.

Eighteen of the 28 patients (65%) remitted in one of the five phases of the study, plus five additional patients with open post-study treatment (total remitting: 82%). Seventy-eight percent of those who remitted, maintained their good benefit for at least six months. A total of 13 (46%) responded to treatment with tranylcypromine (total step 1 and 2).
By study phase: Seven of 27 (26%) patients achieved remission with initial dosing of tranylcypromine up to 60 mg/day, 6/20 (30%) with tranylcypromine doses up to 120 mg/day and 1/6 (17%) to adding dextroamphetamine. Two out of 11(18%) achieved remission with nortriptyline + lithium, and 2/5 (40%) when phenelzine was added. Mean end tranylcypromine dose was 56±12 mg/day (range 10-60) during step 1 and 105 ± 20 mg/day (range 60-120), in step 2.

- Clinical trials in TRD patients who failed at least one antidepressant agent

There are 6 studies published using tranylcypromine in TRD patients who had not responded to at least 1 treatment of adequate dose and duration with an antidepressant. These studies are shown in Table 2. They are listed in chronological order and only the efficacy results of these trials are described.

Table 2. Clinical trials in TRD patients who at least failed one antidepressant agent

Trial (reference)	Study type	Criteria	Resistant to prior medication	Tranylcypro-mine Mean daily dose (range)	Definition of response to treatment	Response rates	Comparator	Response rates
Small et al (1981)	AC single blind parallel	Feighner Diagnostic Criteria for Major Affective Disorder-Depression	1 previous course of TCAs. In addition: 13 failed ECT 5 failed prior MAOIs 16 failed lithium	not provided (range 20-30)	not provided	2/10 (20%) partial or complete relief of symptoms	molindone	5/10 (50 %) partial or complete relief of symptoms
Thase et al (1992a)	Un-controlled open-label	DSM-III	1 previous course of imipramine. In addition: 27 (64%) also failed T3 and/or lithium augmentation strategies	38.5 mg/day (range 20-60)	a reduction of at least 50% on the HRSD + final HRSD≤ 10, which was sustained for at least 2 consecutive weeks. For 6 patients who began with HRSD=10-14: HRSD≤ 6 for at least 2 consecutive weeks	23/40 (58%) Combined results of 36 tranylcypromine and 4 phenelzine treatments		
Thase et al (1992b)	AC double-blind crossover	DSM-III	- tranylcypromine patients: 1 previous course of imipramine - imipramine patients: 1 previous course of tranylcypromine	47.5 mg/day (range 40-60)	a moderate or marked improvement on the CGI (scores of 2 or 3) that was sustained for at least 2 weeks	9/12 (75%)	imipramine	1/4 (25%)
Nolen et al (1993)	AC double-blind	DSM-III(-R)	1 previous course of maprotiline or nortriptyline	84.7 mg/day (range 40-100)	a reduction of at least 50% on the HRSD	5/17 (29.4%)	brofaromine	10/22 (45.5%)
Birken hager et al (2004)	AC double-blind	DSM-IV	- 23 (30%) were non-responders to imipramine or fluvoxamine followed by lithium addition. - 54 (70%) were non responder to a TCA	60.5 mg/day (range 30-100)	a reduction of at least 50% on the HRSD	17/39 (44%)	phenelzine	18/38 (47%)
Adli et al (2008)	Retro-spective chart review	Chart report: ICD-10	an average of 3.3 (range: 1-8) treatment courses	51.9 mg/day (range 20-100)	Remission: a CGI-I score of 1 or an HRSD-21≤ 9 Response: a CGI-I score of 2 or a reduction of at least 50% on the HRSD-21 without fulfilling the remission criteria	26/32 (81%) Of which: 7/32 (21.9%) partial responders 19/32 (59.4 %) remission		

Response and remission rates ranged from 20-81% with mean daily dose of tranylcypromine ranging from 20-80 mg/day. These studies are not considered to be proof of efficacy of tranylcypromine in TRD patients, as the patients did not fail two prior antidepressant agents. Nevertheless, they indicate that tranylcypromine can show efficacy in patients who have failed one prior antidepressant agent.

- Electroconvulsive therapy

With regard to electroconvulsive therapy, the MAH argues that tranylcypromine is a more feasible alternative for treating TRD than ECT, given the stigma and known adverse effects of ECT and the already existing guidance from the Dutch Association of Mental Health and Addiction Care (*GGZ*), as well as the known safety profile and effectiveness shown for MAO inhibitors.

- Functioning as secondary efficacy parameter

Although the Hamilton Depression Scale includes an item on work and activities, none of the literature reported scores from this item specifically. Likewise, despite the Axis V of the DSM including global assessment of functioning, none of the literature reports any changes from start to end of treatment. The few studies that included secondary efficacy parameters, are summarized in table 3.

Table 3: Secondary efficacy parameters

Trial (reference)	Secondary parameter(s)	Response to secondary parameter(s)
Nolen et al (1988) Study 1	None reported	-
Nolen et al (1988) Study 2	None reported	-
Amsterdam (1991)	None reported	-
Volz et al (1994b)	Item 1 of the HAM-D -	Mean reduced by 1.72
	50% drop of the HAMD total score	Mean 56.5% reduction
	Von Zerssen total score (Bf-S)	Mean reduced by 16.36
	Overall evaluation of efficacy	60.87% “very good”
McGrath et al (2006)	Quick Inventory of Depressive Symptomatology - Self-Report	Change (mean) -6.2 %
Stewart et al (2014)	Beck Depression Inventory CGI	Not reported
Small et al (1981)	Hamilton Psychiatric Rating Scale for Depression	Average score reduction 25%
	Hamilton Anxiety Scale	Average score reduction 35%
	Nurses' Observation Scale for Inpatient Evaluation	Average score reduction 28%
	Self-Rating Symptom Scale	Average score reduction 21%
Thase et al (1992a)	None reported	
Thase et al (1992b)	Beck Depression Inventory	% Change (mean) 47.3
	Reversed Vegetative Symptom Scale	% Change (mean) 52.5
Nolen et al (1993)	HDSS	10 (45.5%)
Birkenhager et al (2004)	CGI-Change Score	16 (41%)
	Final HAM-D Score ≤ **7** (remission)	7 (18%)
Adli et al (2008)	HAM-D-21	Mean reduction by 12.8

HDSS: Hamilton Depression Subscale;
HAM-D: Hamilton Depression scale (=HRDS)

IV.4 Clinical safety

Adverse effects commonly associated with MAO inhibitors include orthostatic hypotension and dizziness. Other common adverse effects include headache, dry mouth, constipation, nausea and vomiting, oedema, drowsiness, weakness and fatigue, agitation, nervousness, euphoria, restlessness, insomnia, and convulsions.
Psychotic episodes, with hypomania or mania, confusion, hallucinations, or toxic delirium, may be induced in susceptible persons [Martindale (2011b)].

Sweating and muscle tremors, twitching, or hyperreflexia may occur, as well as blurred vision, nystagmus, urinary retention or difficulty in micturition, arrhythmias, rashes, leukopenia, sexual disturbances, and weight gain with inappropriate appetite.
Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.
Tranylcypromine has a stimulant action and insomnia is a common adverse effect if it is taken in the evening [Martindale (2011a)].

O'Brien et al (1992) studied blood pressure effects and reported that, even though only low dosages (mean dose 18.5 mg) could be given in that study due to side effects, a significant fall in diastolic blood pressure in the standing position was noted and orthostatic hypotension was frequently observed.

Hypertension can occur with MAO inhibitors as a part of a serotonin syndrome. A hypertensive crisis, sometimes fatal, may occur if a MAO inhibitor is taken with some other drugs or tyramine-rich foods ('cheese reaction'). These reactions are characterised by severe headache and a rapid and sometimes prolonged rise in blood pressure followed by intracranial haemorrhage or acute cardiac failure [Martindale (2011b)]. A hypertensive crisis has been described in 2 patients after only one dose of tranylcypromine [Gun et al (1989), Cook et al (1990) in Martindale (2011a)]. In the first case it was thought possible that an auto-interaction may have occurred between tranylcypromine and amphetamine to which it is partly metabolised. In the second case a phaeochromocytoma was found.

Tranylcypromine-dependence with tolerance has been reported in patients with or without a history of previous substance abuse. This is thought to possibly be associated with craving for the amphetamine metabolite. Withdrawal effects after abrupt discontinuation include delirium, sometimes with thrombocytopenia, also after use of lower dosages. Also rapid relapse of depression may occur.

Tranylcypromine has been shown to be porphyrinogenic in animals [Martindale (2011a)].

No study-data have been submitted regarding children or elderly.

Overdose
Gahr et al (2013a) reviewed 20 reports of tranylcypromine overdose in literature (including 10 fatalities). Frequent findings were disturbance of consciousness/cognitive dysfunction (90%), cardio-vascular symptoms (55%), hyperthermia (50%), respiratory distress (45%), delirium (45%), muscular rigidity (30%) and renal failure (20%). The average intoxication-dose was 677 mg. The highest survived dose was 4000 mg and the lowest fatal dosage was 170 mg.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tracydal.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hypertensive crisis Occurrence of convulsion Orthostatic hypotension Serotonin Syndrome
Important potential risks	Exposure during pregnancy Suicidal ideation, suicidal behaviour and acute toxicity Withdrawal reactions (including delirium)
Missing information	Exposure through human milk Exposure to children and adolescents (<18 years old) Renal toxicity

The RMP is acceptable. For the important identified risk 'hypertensive crisis' educational material in the form of a booklet including dietary advice and a patient alert card has been developed. The

material should be distributed to psychiatrists and psychiatrists in training, who will provide the patient with the patient material.

A registry study will be performed to monitor the effectiveness of the educational material and the overall occurrence of adverse drug events.

An interim analysis of the registry study will be performed yearly. At the end of the 2-year study period, the dataset will be evaluated to determine whether the educational material provided to patients and prescribers was effective. The study synopsis is included in the RMP, however the final study protocol should be submitted within three months after authorisation.

IV.6 Discussion on the clinical aspects – benefit-risk assessment

Discussion
Tranylcypromine, a classic non-selective 'irreversible' MAO inhibitor, has a mode of action different from most other antidepressant treatments that are available in the Netherlands. Therefore, it may serve as an alternative for patients not responding to conventional treatments such as SSRI, SNRI and TCA and may be more efficacious as compared to the reversible MAO-inhibitor moclobemide.

A number of pivotal small-scale studies with tranylcypromine for treatment-resistant depression are available from published literature. In a small randomised, double- blinded trial by Nolen et al. (1988), tranylcypromine was compared to nomifensine (a noradrenergic and dopaminergic antidepressant drug not marketed anymore since 1986) and 5HTP **(**5-Hydroxytryptophan**,** neither marketed in the Netherlands**)**. The mean daily doses of tranylcypromine in these studies were around 70-80 mg/day. The overall results of the two studies is that of the 45 patients who were treated with tranylcypromine, 26 (58%) responded within 4 weeks while these results lasted for at least 6 months for 22 (49%). The comparators 5HTP and nomifensine showed only responder rates of 0-10% with an effect lasting less than 6 months.
In two open-label, non-randomised studies, remission responder rates of approximately 50% were reported in treatment resistant patients. In one randomised, double-blind study, similar remission rates were achieved as compared to the comparator brofaromine, an experimental drug with selective MAO inhibitor and serotonergic properties which has never been presented for marketing authorisation (Volz et al).

The studies show several methodological flaws and uncertainties such as:
- it is questioned whether subjects were adequately pre-treated with two or more antidepressants at a proper dose and duration – according to modern treatment standards.
- the chosen active comparators were not registered in Europe for the treatment of depression. Therefore, it is difficult to draw conclusions regarding the clinical relevance of the outcomes of the active-controlled studies, even if superiority or non-inferiority is shown to those unlicensed and non-established active comparators. A comparative study with the only established alternative treatment option, ECT, is lacking.
- no placebo control was included in the active-compared studies, questioning assay sensitivity.
- the majority of the studies were non-blinded.

Furthermore, publication bias of negative studies is not excluded. No dose finding studies were provided. The maximum daily dose stated in the SmPC is restricted to 60 mg.

McGrath et al (2006), as a part of the STAR*D study, compared the effectiveness and tolerability of tranylcypromine and combination treatment with extended-release venlafaxine and mirtazapine in an open-label study in 109 patients with treatment-resistant major depression whose current depressive episode had not responded adequately to treatment in three prior prospective medication trials. Remission rates were not significantly different between the two treatment groups (6.9% for the tranylcypromine group and 13.7% for the venlafaxine plus mirtazapine group). Tranylcypromine was associated with significantly less symptom reduction and greater attrition due to intolerance. The authors concluded that the lower side effect burden, lack of dietary restrictions, and ease of use of venlafaxine and mirtazapine suggest that this combination may be preferred over tranylcypromine.

Though the available reports on studies using tranylcypromine show methodological flaws, it is acknowledged that there is a medical need for patients with major depression not responding to other

pharmacological treatments, and that the use of tranylcypromine is well-established in this specific patient group.

The studies referenced by the MAH indicate a risk of orthostatic hypotension, agitation and sleeplessness, and a low risk of agranulocytosis. The use of classic MAO inhibitors is associated with a risk of potential serious or even fatal hypertensive crisis ('cheese reaction'), in case of failure to adhere to dietary tyramine restrictions. The precautionary measures of a tyramine restricted diet are extensive, and may be difficult to follow for some patients groups. There may be a risk of abuse and overdose because of the stimulating effects of MAO inhibition by tranylcypromine. Reports of these potentially severe adverse effects over several decades of use of this substance on 'named patient' basis are very sparse and non-fatal. Still, the risk dictates use of this product only in case of unmet medical need, i.e. patients non-responsive to alternative anti-depressant treatments including augmentation strategies.

Conclusion
In the Board meetings of 30 October 2014, 30 July 2015 and 12 August 2015 the submitted dossier was discussed. The Board acknowledges that there is an unmet medical need and that treatment with tranylcypromine may be beneficial in a group of patients with major depression who have shown irresponsive to multiple standard anti-depressive treatments, which is not uncommon. The other available treatment option is ECT, which has several side effects such as amnesia.
Although the studies were not considered adequately designed to indisputably confirm efficacy in the target population, the use of tranylcypromine in depression is well-established in Dutch clinical practice, in line with national and international treatment guidelines. At present, more is known on how to prevent tyramine-food interactions and drug-drug interactions than a few decades ago.

The Board agreed that the indication should be restricted to a *last resort* patient population. Augmentation therapy with e.g. lithium is recommended before considering a MAO-inhibitor in the national guideline (*Nederlandse Multidisciplinaire Richtlijn Depressie, 2013*). The data of the STAR*D study indicated that the efficacy of tranylcypromine may be less than the combined treatment of venlafaxine + mirtazapine in patients that did not respond to SSRI and subsequent TCA treatment. Therefore, the indication was restricted to patients not responding to augmented treatment.

Overall the Board concluded that a marketing authorisation can be granted for Tracydal, provided the MAH applies the required risk minimisation measures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The success criteria were met: more than 90% of the participants were able to find the requested information, and of those, more than 90% were able to understand the information that was found and would act appropriately.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tracydal 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality. No new studies were conducted. Clinical and non-clinical overviews of scientific literature were assessed.

Based on the totality of data the MEB came to a positive benefit/risk assessment. Despite the lack of confirmatory randomized placebo-controlled trials, the Board considers that there is a role for tranylcypromine in the treatment of patients with treatment-resistant depression. Its medicinal use can be considered well established. Tranylcypromine is recommended in Dutch and international treatment guidelines as third or fourth line treatment option in treatment-resistant patients with severe depression, not responding to at least two other treatments. The Risk Management Plan covers the important identified and potential risks, and the areas of missing information.

The marketing authorisation for Tracydal was granted on 15 December 2015. The following conditions for marketing authorisation (in accordance with article 21a of Directive 2001/83) have been laid down:

- Additional risk management measures
  - Educational material for patients
  - Patient alert card

A registry study will be performed to evaluate whether the educational material provided to patients and prescribers was effective.
The final study protocol needs to be submitted within three months after authorisation.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

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