LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Abbonate
(tranylcypromine sulfate)

SE/H/2485/01/MR

This module reflects the scientific discussion for the approval of Abbonate. The procedure was finalised on 2022-06-30. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Abbonate, 20 mg, film-coated tablet.

The active substance is tranylcypromine sulfate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Abbonate, 20 mg, film-coated tablet, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Abboxia AB applies for a marketing authorisation in Sweden through a National Procedure.

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology

A lengthy review of possible effects of antidepressants, including tranylcypromine, on uptake and release of neurotransmitter, trace amines and amino acids and their receptors and possible secondary pharmacodynamics including effects on phospholipids and lipid-mediators, lysine-specific demethylase was provided by reference to review publications without submission of the original publications. The mechanism of action in the proposed indication is however not clearly explained or demonstrated.

For a well-established use application this could be acceptable for the non-clinical dossier with reference to clinical use and experience. Further non-clinical pharmacology documentation is not considered necessary.

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).

As with a number of other antidepressants tranylcypromine inhibited rat liver tryptophan pyrrolase activity and produced elevations of brain tryptophan after both acute and chronic administration of the drugs. An increase in the brain levels of tryptophan in rodents at short intervals after the administration of high doses of tranylcypromine has been reported. The findings 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.

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.

The substrates of MAO-A (serotonin, norepinephrine, dopamine, and tyramine) and MAO-B (dopamine, phenylethylamine, and tyramine) are increased in brain and other tissues following tranylcypromine exposure. For example, serotonin levels are 1.4- and 2.3-fold higher after acute and chronic tranylcypromine exposure, respectively. In another ex vivo study, rat brain serotonin increased to 3.2-fold of pretreatment values with chronic tranylcypromine administration compared to only 1.6-fold after chronic moclobemide treatment. Increased serotonin in the CNS after tranylcypromine was also confirmed in an in-vivo PET-study of radio tracer binding to serotonin transporter (SERT) of rats and monkeys. Trace amines, such as phenylethylamine, may even rise over 10- fold. This may be important for tranylcypromine because the role of trace amine-associated receptors in neuropsychiatric disorders is increasingly acknowledged. The oxidized neurotransmitter metabolites are decreased to approximately 30% of pre-dose levels, including 5-hydroxyindole-3-aceticacid, 3,4-dihydroxyphenylaceticacid, and 3,4-dihydroxymandelicacid, which are metabolites of serotonin, dopamine, and norepinephrine, respectively. Hydrogen peroxide and hydroxyl radicals as oxidation by products are also decreased leading to reduced oxidative stress.

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 b-adrenoreceptors in rat brain cortex has been reported after the acute and chronic administration of phenelzine and the chronic administration of tranylcypromine.

Chronic administration (21 days) of phenelzine and tranylcypromine (5 mg/kg per day each) to rats produced a down-regulation of both b1- and b2-adrenoceptors in some areas of the brain. Chronic administration (28 days) of tranylcypromine (1 mg/kg per day) or phenelzine (5 mg or 10 mg/kg per day) resulted in b1- but not b2-adrenoceptor down-regulation in the cortex and cerebellum; a similar result was reported 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 b-agonist salbutamol (3 mg/kg i.p.). Using clonidine as the pharmacological probe, studies on a2-receptor functioning have been conducted on rats and have indicated that tranylcypromine and phenelzine both cause a downregulation of a2-adrenergic receptors after chronic administration. reported An up-regulation of GABAB receptors in the frontal cortex of rats after chronic administration of the MAO inhibitor pargyline has been reproted, but another publicatiob reported that phenelzine did not affect GABAB receptor density or functioning, as measured in neurochemical and behavioral experiments, respectively. 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. Binding studies have demonstrated a down-regulation of 5- HT2 receptors in rats' brains after the chronic administration of tranylcypromin. Based on comprehensive electrophysiological studies it was 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. Chronic administration of phenelzine or tranylcypromine results in the down-regulation 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 (MAO inhibitors were not tested).

The chronic administration of tranylcypromine or phenelzine, at relatively low doses sufficient to down-regulate b-adrenergic and tryptamine receptors, has been found to produce no down-regulation of 3H-flunitrazepam receptors in the cortex of rats; similar negative results were obtained with tranylcypromine (at an i.p. dose of 5 mg/kg b.i.d. for 21 days).

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, but the effect is more rapid with the high dose; and 2. a high dose of tranylcypromine produces a greater decrease in 5-HT2 receptor number in the cortex than the low dose.

Pharmacokinetics

Hippuric acid has been reported as a metabolite of tranylcypromine. The presence of the N-acetyl and ring hydroxylated metabolites of tranylcypromine have been demonstrated in rats' brains. The

formation of N-acetyltranylcypromine and also identified N-acetyl-4-hydroxy-tranylcypromine as a tranylcypromine metabolite in rats' urine has been confirmed.

The pharmacokinetic information provided is limited to some aspects on metabolism and possible CYP inhibition. For a well-established use application this could be acceptable for the non-clinical dossier with reference to clinical use and experience. Further non-clinical pharmacokinetics documentation is not considered necessary.

Toxicology

Repeat dose toxicity

TCP was first synthesized in the 1940s as an amphetamine analogue but was not further investigated for the next 10 years due to low amphetamine-like activity. Retesting it as a MAO inhibitor revealed high activity against this new target and led to more pharmacological studies in animals and humans. TCP was therefore one of the earliest representatives of modern psychopharmacology. The first clinical study using TCP was published also in 1959. Tranylcypromine is almost 80 years old and repeat-dose toxicity studies according to current guidelines have not been conducted. Since 1959 it has been used on and off in the clinic.

Genotoxicity and carcinogenicity

Data on genotoxicity is limited. The first screening for mutagenic effect of the most widely used psychotropic drugs including tranylcypromine has been reported. Nineteen drugs selected from different groups, some of them presenting a chemical structure similar to well-known mutagens and carcinogens, were tested with Salmonella/microsome test. With the exception of nialamid, they didn't show any mutagenic effect both in the presence and in the absence of rat liver enzymatic activation. The effects of acute (24 h) exposure to the antidepressants amitriptyline, imipramine (both tricyclics), fluoxetine (a selective serotonin re-uptake inhibitor) and tranylcypromine (a monoamine oxidase inhibitor) on DNA damage in cultured C6 rat glioma cells were determined using an alkaline comet assay. The effects of manipulation of intracellular cyclic AMP by pretreatment with dibutyryl cyclic AMP (dBcAMP) and 3-isobutyl-1-methylxanthine (IBMX) were also studied. For fluoxetine, the effects of addition of exogenous glutathione (GSH) and pretreatment with L-buthionine sulfoximine (BSO) were also assessed. There were increases in DNA damage with increasing concentrations of antidepressants. IBMX pretreatment protected against antidepressant-induced DNA damage in C6 cells pretreated with dBcAMP. Addition of exogenous reduced GSH and BSO increased DNA damage after fluoxetine exposure. The data show that the antidepressants induce significant amounts DNA damage in C6 cells.

The assay for DNA damage by antidepressants in C6 glioma cells is a non-standard assay and difficult to interpret. However, in another publication, 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.

In literature there was no evidence found on carcinogenicity of tranylcypromine.

Developmental and reproductive toxicity

On the day before ovulation in rats, there exists a critical period before which hypophyaectomy or barbiturate injection blocks ovulation and after which both procedures are ineffective. It is thought that a stimulus arises in the brain on the day of proestrus which causes pituitary release of luteinizing hormone with subsequent stimulation of ovulation by the ovary. It has been found that tranylcypromine, an inhibitor of brain amine oxidase, given before this critical period, blocks ovulation. Rats were exposed to light from 7 a.m. to 7 p.m. those with regular 4-day vaginal estrous cycles were injected i.p. during proestrus with pentobarbital (30 mg/kg), tranylcypromine (10 mg/kg), or solvent (saline). On the following day, ova in the Fallopian tubes were counted. Control rats (saline) ovulated 9-15 ova (ave., 11.9). Rats given pentobarbital at 10 a.m., 12, 1, 2, 3, and 4 p.m. averaged

12.3, 10.0, 9.4, 6.0, 3.6, and 10.4 ova/rat, respectively. Corresponding values for tranylcypromine were 0, 0, 0, 6.2, 6.9, and 8.2, respectively, and at 5 p.m., 13.2 ova/rat. Brain serotonin increased to 230% and norepinephrine to 140% of normal at 3 p.m. after injection of tranylcypromine at 1 p.m. Brain amine levels are being investigated in normal animals throughout the estrous cycle.
Although risk was suggested in consecutive pregnancies from one woman, the human pregnancy experience is too limited to assess adequately the embryo-fetal risk.

Fetal risk summary

Relevant animal reproduction data have not been located. However, the drug crosses the rat placenta. It is not known if tranylcypromine crosses the human placenta. The molecular weight (about 365) is low enough that exposure of the embryo-fetus should be expected.

Monitoring data of 21 mother-child pairs exposed to monoamine oxidase inhibitors during the 1st trimester, 13 of whom were exposed to tranylcypromine is available. Three of the 21 infants had malformations (relative risk 2.26). Details of the 13 cases with exposure to tranylcypromine were not specified.

A brief 2000 abstract described two consecutive adverse pregnancy outcomes in a woman treated with tranylcypromine. In the first pregnancy, the 41-year-old woman with severe depression was treated with tranylcypromine (100 mg/day), pimozide (1 mg/day), and diazepam (5-10 mg/day). The woman delivered a stillborn fetus at 31 weeks' gestation. Examination of the macerated female fetus revealed hypertelorism, a large atrioventricular septal defect, single coronary ostium, and right pulmonary isomerism. The placenta had multiple infarcts that were considered significant factors in the fetal death. In her second pregnancy (other drugs and doses not specified), an ultrasound at 19 weeks' revealed a fetus with a head described as "lemonshaped." A female infant (normal karyotype) was delivered at 38 weeks because of poor growth (weight not specified). The infant had multiple defects, including hypertelorism, low-set overfolded ears, cleft palate, micrognathia, marked distal phalangeal hypoplasia, agenesis of the corpus callosum, and an atrioventricular septal defect (first detected at 26 weeks'). The outcomes of both pregnancies were attributed to tranylcypromine, possibly due to reduced uterine and placental blood flow.

Breastfeeding summary

No reports describing the use of tranylcypromine during lactation have been located. The molecular weight (about 365) is low enough that excretion into breast milk should be expected.
The effect of this exposure on a nursing infant is unknown.
Use of any drug in pregnancy, during lactation or in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to mother and child. Animal reproductive studies show that tracydal passes through the placental barrier into the fetus of the rat, and into the milk of the lactating dog. The absence of a harmful action of tracydal on fertility or on postnatal development by either prenatal treatment or from the milk of treated animals has not been demonstrated. Tranylcypromine is excreted in human milk.
Although data on Developmental and reproductive toxicity are very limited, there are some signals of teratogenic potential. However, the data are too limited to conclude on the reproductive toxicity potential.

Overall conclusions on toxicology

A review of available scientific literature data has been provided. From the data it can be concluded that tranylcypromine is not likely to be mutagenic. No data on carcinogenic potential has however been located.

Relevant animal reproduction data have not been located. Tranylcypromine crosses the rat placenta. Tranylcypromine is excreted in human milk. Although data on developmental and reproductive

toxicity are very limited, there are some signals of teratogenic potential. However, the data are too limited to conclude on the reproductive toxicity potential. The lack of data is reflected in the SmPC section 5.3. Adequate recommendations during pregnancy and lactation are provided in section 4.6.

Excipients and impurities

For the composition of the product under consideration Tranycypromine 20 mg tablets, the following excipients were used: cellulose microcristalline, calcium hydrogen phosphate anhydrous, starch pregelatinized, silica colloidal anhydrous, talc and a color coating system.

The levels of impurities are according to in-house specifications.

Environmental Risk Assessment (ERA)

The environmental assessment of the presented product is discussed based on the considerations in the guidance document EMEA/CHMP/SWP/4447/00 “Guideline on the environmental risk assessment of medicinal products for human use”. This application is for a well-established product containing the active substance tranylcypromin.

Conclusion

Based on the results of the Phase 1 and PBT assessment it can be concluded that no environmental concerns are apparent, and it can be assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

IV. CLINICAL ASPECTS

Pharmacokinetics

Absorption

Tranylcypromine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 3 hours after ingestion. The bioavailability of tranylcypromine is not reported in the literature. For patients on chronic oral tranylcypromine, a mean peak plasma level of 112 ng/mL was measured following a single dose of 20 mg tranylcypromine 2 h after ingestion.

Distribution

A volume of distribution of 1.1 - 5.7 L/kg body weight can be assumed. It is known that tranylcypromine is excreted in human milk. There are no known findings on the impact on foetal circulation.

Biotransformation

Primary products of hepatic biotransformation are p-hydroxytranylcypromine and N-acetyltranylcypromine. Only about 4% of the dose is found in the urine as unchanged tranylcypromine.

Elimination

A half-life of approximately 2.5 h was found in a study with depressive patients after a single dose of 20 mg tranylcypromine. Excretion takes place mostly in the form of metabolites (hippuric acid and benzoic acid) via the bile and mainly the kidneys. Renal tranylcypromine excretion is highly dependent on the pH value; low pH values promote excretion.

Stereoselectivity

Trancylpromine is a stereoisomeric substance where the enantiomers exhibit markedly different pharmacokinetic properties. The plasma concentration of the (-) isomer always exceeds that of the (+)

isomer. Studies indicate that no in vivo racemisation occurs.

Interactions
In vitro, trancylpromine is a competitive inhibitor of CYP2A6 at clinically relevant concentrations (Ki 0.08 μM). Trancylpromine also inhibits CYP2C19 in vitro with a Ki of 32 μM this is not likely clinically relevant. No discussion of trancylpromine as a victim for pharmacokinetic interactions has been provided.

Overall conclusions on pharmacokinetics

For a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial. The Applicant has provided a thorough bridging discussion. Briefly, trancylpromine is a highly soluble substance, though its bioavailability is unknown. Thus it is either a BCS-class 1 or 3, but which cannot be concluded with the available data. As a conservative approach BCS-class 3 could be assumed. Further it is discussed that although the qualitative and quantitative composition of Abbonate is not exactly the same as any product described in the literature none of its excipients are known to affect the absorption. Still, a formal BCS-biowaiver is not applicable for Abbonate. Several different products have been used in the literature supporting efficacy and safety of which two are approved products, one in EU and one outside the European market. The dissolution profile of Abbonate is similar to one of these products (the one on the European market) while the other product has a markedly different profile. The different dissolution profiles of two approved products indicate that in vitro drug release is not critical for the efficacy and safety of tranylcypromine. Further, the dose is titrated individually based on the patients' clinical response making potential differences in absorption due to formulation less critical. However, if these differences in dissolution profile could translate into differences in pharmacokinetics that could have a negative impact on a patient on a stable dose of one product switching to Abbonate cannot be entirely discarded. It is still reassuring that Abbonate is similar to at least one product described in the literature which is also an approved product in use on the European market. In conclusion trancylpromine is a highly soluble drug and Abbonate show a rapid dissolution in vitro, similar to another approved product on the European market. None of Abbonate's excipients are known to affect absorption and the dose is titrated individually. Overall, it is considered that a sufficient bridge to the literature is established.

The basic pharmacokinetic parameters of trancylpromine are generally only briefly described by the Applicant and the data mainly supported by review articles. Information regarding the enzymes involved in trancylpromine metabolism is missing as is PK information regarding known active metabolites. Likely this information is not available in the literature and the lack of knowledge has been accepted for other approved trancylpromine products.

Pharmacodynamics
According to the Applicant, the antidepressive effect of tranylcypromine is due to elevation of the norepinephrine (NE), dopamine (DA) and 5-hydroxytryptamine (5-HT, serotonin), by inhibiting the main enzymes of their degradation, monoamine-oxidas A and B. Tranylcypromine does not appear to inhibit aminoxidases other than monoamineoxidase (MOA). In addition to inhibition of MAO, Tranylcypromine inhibits lysinespecific histone demethylation type 1 and interacts with the endogenous cannabinoid system.

The Applicant has provided an overview where the overall data are not indicating any possible genetic differences related to the pharmacodynamic response of the product.
Concerning laboratory findings in tranylcypromine treatment in TRD, risk of abuse, withdrawal phenomena and TCP-related thrombocytopenia was mentioned.

Overall, the Appplicant has presented limited information on pharmacodynamics and on laboratory findings. It could be that further information is not available in the literature and the lack of knowledge has been accepted for other approved trancylpromine products.

Clinical efficacy

Literature search

The Applicant has provided a clinical overview largely based on published scientific literature, searched in bibliographic databases. Specific search criteria were used, adjusted to the specific database terminology, scope and structure, covering all aspects required for this overview. Primarily English language peer-reviewed literature was selected initially on the basis of search results including abstracts, and subsequently on the basis of original publications acquired. Where necessary reference lists of original publications were searched manually for complementary publications.

Clinical efficacy

For background, recent studies suggest that delaying the treatment of MDD can result in progressive damage to brain areas associated with depression, and that pharmacotherapy may halt or reverse those effects. In cases of insufficient response, early change of treatment is important to achieve the best possible outcome for the individual patient.

Definitions of the patient group TRD

The definition of treatment resistant depression (TRD) in the current CPMP guideline: "*TRD 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*".

There is no place for tranylcypromine in first-line treatment, due to the safety profile.

The Applicant's selection, analyse and critical discussion of main studies to provide efficacy and dosage data have been presented as main studies and additional supportive studies:

- **6 main studies** in patients who have treatment resistant depression which at least failed two different antidepressant agents, with tabulated data. Primary endpoint usually was 50% reduction in symtom scale Hamilton Rating Scale for Depression (HRSD).
- **6 supportive studies** in a wider group of treatment resistant patients: those who failed at least one antidepressant agent. Primary endpoints varied such as HRSD, CGI.

Summary of main studies

Out of 6 selected small main studies, two were presented by the Applicant as more relevant. The first was open-label with crossover for non-responders, in total 26 patients eligble to exposure. The second was double-blind (randomisation methods unknown) with crossover for non-responders, in total 21 patients eligble to exposure. Mean daily doses were 70-80 mg/day. For initial inclusion, at least 18 points of the Hamilton Rating Scale for Depression (HRSD) was required. Primary endpoint was the HRSD scale, for response a 50% reduction was required on the HRSD scale, in comparison to baseline (i.e. before first treatment in a preceding study of oxaprotiline or fluvoxamine, from which only non-responders could proceed to tranylcypromine). No secondary endpoint was described.
In summary, out of in total 45 patients treated with tranylcypromine, 26 (58%) were responders within 4 weeks and 22 (49%) after 6 months. Somewhat similar results were shown in an uncontrolled open label study with a mean daily dose of 128 mg, 50% were complete responders and 21% partial

responders. Later in an uncontrolled open label study, mean doses 56 mg and 105 mg in 2 steps, overall 46% responded. As a later study found responder rates over 70% for both tranylcypromine and the comparator brofaromine, it was presumed those patients had not been correctly classified or had not received adequate treatment.

Overall, based on the Applicant's detailed discussion of efficacy main studies, though data are scarce it appears that in TRD patients who have failed at least two treatments with antidepressant agents, tranylcypromine has been effective in at least 50% of the treatment resistant patients receiving the medical product.

To note the presented main studies include treatment with tranylcypromine after failure of treatment with at least two antidepressants and do not include e.g. lithium augmentation, which however is included as additional prerequisite in the indication. The requirement of e.g. lithium augmentation as a third step before initiating tranylcypromine is in line with practice and national and international guidelines (see justifications below).

Whereas the selection of non-responding patients thus is repeated in the third treatment step of augmentation before use of tranylcypromine, there is little such study data to assess. Therefore, there is substantial uncertainty regarding the proportion of responders with the actual indication (including required use of e.g. lithium augmentation).

Supportive studies
There were 6 studies published using tranylcypromine in patients who had not responded to at least 1 treatment of adequate dose and duration with an antidepressant. Response and remission rates ranged from 20-81%, with mean daily dose of tranylcypromine ranging from 20-80 mg/day. These studies suggest efficacy in patients who have failed at least one prior antidepressant agent.

Recent meta analysis data is considered to support recognised efficacy and acceptable safety in TRD when defined by the Applicant's main studies criteria, provided a maximum dose level of 40-60 mg.

Data to support dose recommendations
Based on very limited data, there is some support for a maximum dose of 40-60 mg. There is not sufficient data to support a recommendation for higher doses.

Information on dosage briefly summarised:

- From clinical trials, interpretation is complicated due to heterogenity of studies. Overall there is some consistency in the findings of clinical effect.
- Roughly one third each of trials used:
  -low doses of < 30 mg/day
  -medium doses of 30-60 mg/day
  -higher doses of up to 100 mg/day
- Some reviews conclude optimal response seen in patients who tolerate 40-60 mg TCP.
- 40-60 mg is a maximum dose in previously marketed TCP drug preparations for patients who can be closely supervised.
- No controlled dose finding studies have been conducted.
- No data available for high doses on the long term.

Short-term vs long-term efficacy
The majority of studies are of less than 6 months duration and appear to support a short-term effect.

The Guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev. 2) recommends that initial response to treatment is maintained in at least one study, following a randomized withdrawal design or an extension study for 6 months. The long-term phase is usually set at about 6 months, to correspond with average duration of an episode of depression.

The provided literature does not include studies designed as intended by the guideline. However from studies including follow-up, up to 6 months it appears that the initial response is maintained in a majority of responders to tranylcypromine. Three of the main studies included data on patients in remission after 6 months. One supportive article reports data on patients still in remission after 3 months.

There is some consistency in findings of clinical effect also on long-term. Dose levels used mostly were in the interval 20-60 mg. The data is considered to provide some support of efficacy in the TRD group, defined as in the Applicant's selection of main studies.

Studies of high dose treatment
Whereas the proposed SmPC only recommends dosages of up to 60 mg/day, the applicant has provided some information on trials investigating higher dosage than 60 mg/day. With regards to higher doses, analysis is difficult because few studies provided numerical data for adverse events. Data are considered insufficient to recommend doses higher than 60 mg.

Efficacy - additional justifications

The presented main studies include treatment with tranylcypromine after failure treatment with at least two antidepressants, and do not include e.g. lithium augmentation, which however is an additional prerequisite in the PI. The use of lithium augmentation as a treatment step before initiating tranylcypromine is in line with national and international guidelines.

A tranylcypromine product was approved in Sweden in 2021 via a decentralised procedure with the Netherlands as Reference member state. The indication includes required lithium augmentation, in line with clinical recommendations. Augmentation with lithium before treatment with tranylcypromine is recommended in Dutch clinical practice guideline, based on referenced scientific data. Also other national and international clinical guidelines also recommend lithium augmentation before treatment with tranylcypromine.

In summary, the presented main studies provide support for efficacy in the TRD patient group when defined as in the Applicant's selection of the main studies. Assessment of efficacy in the TRD patient group as defined in the proposed SmPC is more difficult. The lack of main studies with the indication including failed augmentation with e.g. lithium hampers the assessment. Likely such additional main studies are not available in the literature, and the lack of knowledge has been accepted for other approved trancylpromine products. Based on the available data and justifications, it is considered the uncertainty could be acceptable.

Overall it is considered that the Applicant has provided appropriate justifications for efficacy within the proposed indication.

Clinical safety

For Safety assessment, the Applicant has tabulated and briefly discussed 12 studies as relevant for the indication treatment resistant depression, of which were 5 controlled double-blind. The trial populations consisted of males and females. Very few patients with age >65 were included in the trials.
There is little long-term safety data. The longest study duration reported a the TCP group exposure was on average 8 weeks. Overall the application is based on a rather old and limited body of safety data.
The side effects are significant and complex. For example there is very frequent hypotension of unknown mechanisms, and there is risk of severe hypertension with a potentially fatal outcome in hypertensive crisis.
No deaths or other serious adverse events were reported in the trials referred to.
The proportion of withdrawals due to an adverse event in the reviewed clinical studies ranged from 0% up to 70%. In a more recent open label study, 41% of subjects on 8 weeks of TCP 20-60 mg withdrew due to adverse events, and this was higher ($p<0.03$) than in patients on the comparators venlafaxine and mirtazapine.
Orthostatic hypotension was reported as a frequent reason of intolerance to TCP and of study drop-out in several studies.
Regarding cumulated frequencies to support data in SmPC table 4.8, the Applicant refers to early studies reporting frequent adverse events of TCP concerning dizziness, insomnia and overexcitement. One study focusing on adverse effects of TCP found 17% orthostatic hypotension (passing out, falling), 7% hypomania, 5% paresthesias, and 2% hypertensive reactions, confusion, urinary retention, sexual function disorders, and rash.
A review of safety data from relevant scientific literature was included by the Applicant. Average daily exposure to tranylcypromine here ranges from 22-129 mg/day.

According to the Applicant, adverse effects of tranylcypromine are as for MAOIs in general. Adverse effects commonly associated with MAOIs include orthostatic hypotension and attacks of dizziness, headache, dry mouth, constipation and other gastrointestinal disturbances (including nausea and vomiting), and oedema. Drowsiness, weakness, and fatigue are reported frequently although CNS stimulation may also occur and symptoms include agitation, nervousness, euphoria, restlessness, insomnia, and convulsions. Psychotic episodes, with hypomania or mania, confusion, hallucinations, or toxic delirium, may be induced in susceptible persons.

Sweating and muscle tremors, twitching, or hyperreflexia may occur, which in overdosage may present as extreme hyperpyrexia and neuromuscular irritability. Other reported reactions include blurred vision, nystagmus, urinary retention or difficulty in micturition, arrhythmias, rashes, leucopenia, sexual disturbances, and weight gain with inappropriate appetite. Jaundice has been reported with hydrazine MAOIs and, on rare occasions, fatal progressive hepatocellular necrosis. Peripheral neuropathies associated with the hydrazine derivatives may be caused by pyridoxine deficiency.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

MAOIs have been the most commonly implicated drugs in the serotonin syndrome. A severe hypertensive crisis, sometimes fatal, may occur if an MAOI is taken with some other drugs or certain foods. 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.

Tranylcypromine has a stimulant action and insomnia is a common adverse effect if it is taken in the evening. Tranylcypromine has an adverse effect profile similar to those of other MAO inhibitors and although hypertensive reactions are more likely to occur with tranylcypromine than with other MAOIs, severe liver damage occurs less frequently.

Dependence on tranylcypromine with tolerance has been reported in patients receiving high doses with or without a history of previous substance abuse.

Although orthostatic hypotension is more common, hypertension can occur with MAOIs. A hypertensive crisis has been described in 2 patients after only one dose of tranylcypromine. In the first case it was thought possible that an autointeraction may have occurred between tranylcypromine and amphetamine to which it is partly metabolised. In the second case the provocation of hypertension led to the finding of a previously undiagnosed phaeochromocytoma and it was suggested this may have been a possibility in previous reports of hypertension induced by MAOIs.

Serotonin toxicity syndrome
Another potential danger is serotonin toxicity syndrome (ST), which can occur following the combination of irreversible MAOI with a drug which has the potential to elevate 5-HT synaptic levels, such as a serotonin-selective reuptake inhibitor (SSRI). In this context, the relatively long period required for return of MAO activity following cessation of therapy with an irreversible inhibitor is important when a change in therapy is required. If therapy with a SSRI is to be used, there is a danger of ST if these drugs are instituted before MAO activity has returned to normal levels. Following cessation of tranylcypromine administration in healthy subjects, a period of 30 days was required for complete normalization of the pressor response to oral tyramine challenge.

Effects on dreaming
Withdrawal from tricyclic ADs and from the monoamine oxidase inhibitors phenelzine and tranylcypromine may cause nightmares. Acute withdrawal from tranylcypromine overuse caused terrifying nightmares and a REM sleep rebound of up to 76% of total sleep time.

Withdrawal and discontinuation phenomena
Abrupt discontinuation of TCP can cause discontinuation syndromes of different severity. Thus, TCP should be tapered off slowly whenever treatment shall be stopped. Tranylcypromine is a substance of abuse in a small subgroup of patients. Tranylcypromine withdrawal is a rare cause of delirium, usually after abrupt cessation of excessive doses, and is often accompanied by thrombocytopenia; this may be an important clinical hint in cases with delirium of unknown origin.

Withdrawal phenomena (WP, in the case of TCP-abuse/dependence) or discontinuation phenomena (DP, in the case of absent TCP-abuse/dependence) subsequent to abrupt termination of TCP are a

potentially severe clinical syndrome. Even termination of lower daily dosages of TCP may result in delirium. Thrombocytopenia features diagnostic value in patients with deliria of unknown etiology. TCP should be administered with great care, especially in dependence-prone patients.

Tranylcypromine is much less appraised for its risk of abuse, dependence, and the development of discontinuation phenomena including withdrawal delirium subsequent to abrupt discontinuation of normal or excessive doses, as observed in single patients.

Risk of tolerance, abuse, and dependence
Tranylcypromine (TCP) is an effective antidepressant with a complex pharmacological profile and a risk of tolerance, abuse and dependence. This may relate to TCP's chemical similarity to amphetamine and the presynaptic “amphetamine-like" actions of the (-)-enantiomer, in addition to its well-known main effects as a MAOI that are exerted by (+)-TCP.

Withdrawal from TCP is also a rare differential diagnosis of delirium. The coincidence of sudden delirium, thrombocytopenia, liver dysfunction, or steatosis hepatitis has been described in several case reports.

Potential mechanisms for thrombocytopenia in chronic TCP overdose include increased venous pooling in the spleen, excessive MAO inhibition in the thrombocytes, and impaired serotonin uptake by blocking the serotonin transporter in the cell membrane.

Overdose and intoxication
Tranylcypromine features a complex pharmacologic profile and overdose might induce severe intoxications. Symptoms of overdosage of tranylcypromine are as for MAOIs in general and may be minor at first and progress over the ensuing 24 to 48 hours. After mild overdosage and symptomatic and supportive therapy, recovery may occur in 3 to 4 days, but after massive overdosage symptoms may persist for up to 2 weeks. CNS depression and drowsiness have been noted with overdosage, but CNS stimulation is more common, with irritability, hyperactivity, agitation, hallucinations, or convulsions. Respiratory depression and coma may ultimately occur. Cardiovascular effects include hypertension, sometimes with severe headache, although hypotension is more frequently reported; cardiac arrhythmias and peripheral collapse can also develop. Profuse sweating, hyperpyrexia, and neuromuscular excitation with hyperreflexia are also prominent features of overdosage.

Discussion of post marketing safety data

The Applicant has presented an overview of postmarketing ADR data from EU, US and WHO databases. ADRs reported greater than 2% are hypertension, hypertensive crisis, serotonine syndrome and overdose.

Whereas liver effects were rare, as expected there are safety issues concerning interactions with food and in particular risk of severe hypertension (but also hypotension, dizziness and falls), serotonin syndrome and effects from overdose.

It is noted that in the Netherlands, the since 2015 registered tranylcypromine product is prescribed to near 1900 patients yearly with additional risk minimization: information on tyramine restricted diet, and information on how to measure and record blood pressure measurements from the start of

treatment. Although postmarketing data are insufficient for conclusion, if anything the NL data points in the direction of using education materials for risk minimization.

In the proposed RMP the Applicant has added risk minimization measures targeting the interaction with food and risk of hypertensive crisis.

The EMA EudraVigilance database (accessed through www.adrreports.eu) included 879 case reports containing 2486 adverse events on tranylcypromine for the period of January 1995 up to February 2021. From these case reports, 42.5% (374 case reports) originate from outside of the European Economic Area, and 57.5% (505 case reports) originate from within the EEA. Case reports from within the EEA originated from the following countries: Netherlands (264), Germany (197), United Kingdom (21), Sweden (9), Austria (5) and France (4) other (5).
Of the 879 case reports in total in the EudraVigilance database, 2 case reports concerned 0 to 1-month-old infant girls, no reports occurred in children or adolescents, while 543 case reports concerned 18 to 64 years old patients, 156 case reports concerned patients with an age between 65 and 85 years old and the remaining 2 reports concerned patients older than 85 years. Gender was not specified in 31 case reports, 585 cases concerned female patients and 259 cases concerned male patients.
The spontaneous reports originated in 662 cases from health care professionals (HCPs) and 207 cases were received from non-healthcare professionals, so for 10 case reports the reporter group was not specified.

VigiBase (http://www.vigiaccess.org) is the World Health Organisation (WHO) database maintained by the Uppsala Monitoring Centre. It contains reports of adverse drug reactions that have been reported by healthcare professionals such as doctors, pharmacists and patients. It is the largest database of its kind in the world, with over 20 million reports of suspected adverse effects of medicines, submitted, since 1968, by member countries of the WHO Programme for International Drug Monitoring. It is continuously updated with incoming reports. All (S)AEs for tranylcypromine were extracted (VigiAcces (2021). This listing included a total of 4093 (S)AEs on tranylcypromine out of 1845 reports. Case reports originated from Americas (1041), Asia (4), Europe (637) and Oceania (163).

Overall, the relative ratio of events occurring on tranylcypromine use do not differ that much between the different territories, despite overlap in databases (with EudraVigilance containing potential duplicates of the other three consulted databases) and differences in time span of the information included in each specific database. The data therefore appear representative of patients globally including Sweden.

Discussion of data from combined treatments

The proposed product information includes that adding tranylcypromine to specifically amitriptyline can be done in exceptional circumstances, and when taking all necessary precautions while slowly increasing the dose. It appears that non- or low-serotonergic activating TCAs and 5-HT2A antagonists, such as amitriptyline, doxepin, and mianserin as well as trazodone have been found to be relatively safe in combination with tranylcypromine at low to moderate doses. The adverse event profile of the combination treatment with TCA was not worse than for the mono-treatment with amitryptiline.

Thus according to the Applicant, an acceptable safety was shown for adding tranylcypromine to specifically amitriptyline, provided only in exceptional circumstances and when taking all necessary precautions while slowly increasing the dose. A reference in the SmPC to this information is provided.

Discussion of interactions

The Applicant har provided a detailed overview of the serious interactions with medical products and with food, also reflected in the PI.

Interactions with food

Tyramine is a strong indirect sympathomimetic agent that induces the release of norepinephrine enriched in synaptic vesicles and, thereby, precipitates life-threatening hypertensive crisis accompanied by severe headache, chest tightness, pallor, nausea, and sweating ("cheese reaction"). The presence of tyramine, a substrate of MAO-A and MAO-B, in food is not a risk for the normal population because of sufficient MAO activity in gut and liver and a tyramine tolerance of 800–2000 mg per meal. With irreversible MAO-A/B inhibition by tranylcypromine, however, the presence of only 35 mg of tyramine in food (range 20–50 mg) was found to increase systolic blood pressure by 30 mmHg in a preselected population most sensitive to tyramine.

An amount of 25 mg tyramine per meal is regarded as a safety margin for severe reactions and 6 mg as a conservative threshold for the initiation of mild symptoms.
Therefore, the fundamental requirement of TCP treatment is a mandatory tyramine restricted diet.

Lists of foods to be avoided have been improved recently by a critical reappraisal of old clinical and chemical-analytical data as well as reference to modern methods of manufacture and storage of food. In doing so, modern food, including normal servings of bottled/canned beer, wine, distilled spirits, and chocolate are now regarded as less likely to have high tyramine content by some authors. It has also been discussed that the effort needed to maintain a tyramine-restricted diet may have been exaggerated in the perception of some doctors and patients, thus leading to underuse of TCP.

Interactions with medical products

Concerning pharmacodynamic drug interactions, safe treatment with TCP first of all requires the prevention of two principle mechanisms of drug interaction: (i) serotonergic activation by serotonin reuptake inhibitors (e.g. SSRls, SSNRls) or serotonin precursors, and (ii) norepinephrinergic activation by indirect sympathomimetics (e.g. ephedrine, phenylpropanolamine).

With reference to original articles, the Applicant has discussed in detail a number of interactions relevant to common co-morbidity and in relation to certain SmPC sections, including interactions with increasingly prescribed ADHD medication.

Risk Management Plan
The MAH has submitted a risk management plan, 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 Abbonate.

Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns, Table SVIII.1	
Important identified risks	Hypertensive crisis
Important potential risks	*Not applicable*
Missing information	*Not applicable*

Pharmacovigilance Plan

Routine pharmacovigilance is suggested (SmPC sections 4.4, 4.5, 4.8. PL sections 2 and 4)
Additional pharmacovigilance activities are proposed by the Applicant.

Risk minimisation measures

Risk Minimisation Plan V.3

V.1. Routine Risk Minimisation Measures

There are safety concerns for Abbonate. Routine Risk minimisation measures for risks not considered important for inclusion in the safety concerns are presented in section SVII.1.1.

V.2. Additional Risk Minimisation Measures

Patient guide, including patient diary
Patient alert card

V.3. Summary of risk minimisation measures

Not applicable.

Summary of the RMP

The submitted Risk Management Plan, version 0.3 signed 14 December 2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Tracydal 20 mg film-coated tablet, NL/H/4812/001. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application is based on rather old data. The tabulated safety data from publicly available trials is limited and studies were only up to 3-6 months. Efficacy data suggest response of tranylcypromine in 50% of TRD patients who have not responded to least two treatments with antidepressant agents. From other, supportive studies were reported varying response rates. Overall the limited evidence and heterogenicity of study design makes interpretation difficult.

The well-known safety profile include the risk of fatal outcomes of interactions with food, the risk of serotonine intoxication from interactions with medical products, and of serious risks related to overdose. The safety data also indicate risks for e.g. orthostatic hypotension, agitation and sleeplessness, and a risk of agranulocytosis. There is a risk of abuse and misuse because of the stimulating effects of MAO inhibition by tranylcypromine.

Hiatorically the use of tranylcypromine is associated with a well-known risk of potential serious or fatal hypertensive crisis, in case of failure to adhere to dietary tyramine restrictions. The precautionary measures of a tyramine restricted diet are extensive. The approval of this medical product requires conditional patient education materials. The indication should be restrictive and appears to be clinically appropriate and well aligned with other approved products. This includes patient educational material (patient alert card, patient guide) concerning tyramine restricted diet and information on how to measure and record blood pressure measurements from the start of treatment.

Although the studies provided cannot indisputably confirm efficacy in the target population, the use of tranylcypromine in depression is considered well-established since 10 years with an acceptable level of safety. Thus, it is acknowledged that the use of tranylcypromine is well-established in this specific patient group. Based on the presented data from main studies, the added postmarketing data, and that the similar indication and dosage recommendations are found in the SmPCs of other products, there is support for recognised efficacy and acceptable safety.

Provided the indication is restricted to a TRD population for last resort use, with maximum dose 40-60 mg and conditional risk minimisation, the medical product could be recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

Additional risk minimisation measures (including educational material)
The educational material should contain the following key elements:

Patient guide - educational material to describe the dietary restrictions relevant to MAO inhibitors such as tranylcypromine (low-tyramine diet), and blood pressure monitoring.
Includes a **patient diary** for blood pressure measurements.
Objectives:

▪ To describe why and how the risk of hypertensive crisis requires a tyramine-restricted diet and monitoring of blood pressure
▪ To provide explicit and detailed dietary advice for the tyramine-restricted diet which patients must adhere to.
Rationale for the patient guide:
▪ The risk of high-tyramine diet promoting hypertensive crisis is well-known and can be prevented by low-tyramine diet.
Target audience and planned distribution path:
▪ Patients, related household parties, concerned heath care professionals
▪ The materials will be available in MAH web sites to be printed or the printed brochures can be ordered from MAH free of charge.
Plans to evaluate the effectiveness of the interventions and criteria for success:
▪ The effectiveness of the educational material is evaluated regularly based on the received post-marketing data. The frequency of the events related to the important identified risk monitored in a monthly basis and it is thoroughly analysed in biannual signal detection.

Patient alert card - describes that the patient is under MAO inhibitor tranylcypromine treatment.
Objectives:
▪ To be carried by the patient at all times
Rationale for the patient alert card:
▪ To ensure that information of the Abbonate treatment is communicated to healthcare professionals as appropriate.
Target audience and planned distribution path:
▪ Patients, heath care professionals
▪ The materials will be directly readable on MAH web sites, could be printed, or the printed brochures can be ordered from MAH free of charge.
Plans to evaluate the effectiveness of the interventions and criteria for success:
▪ The effectiveness of the educational material is evaluated regularly based on the received post-marketing data. The frequency of the events related to the important identified risk monitored in a monthly basis and it is thoroughly analysed in biannual signal detection.

VII. APPROVAL

Abbonate, 20 mg, film-coated tablet, was approved in the national procedure on 2022-06-30.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/2485/01/MR	Initial Mutual Recognition Procedure	Yes	2024-04-04	Approval	N/A

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se