Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Buspirone Hydrochloride 5 mg Tablets
Buspirone Hydrochloride 10 mg Tablets
Buspirone Hydrochloride 15 mg Tablets
Buspirone Hydrochloride 30 mg Tablets

buspirone hydrochloride

PL 42289/0017-0020

Wave Pharma Limited.

LAY SUMMARY

Buspirone Hydrochloride 5 mg, 10 mg, 15 mg and 30 mg Tablets
buspirone hydrochloride

This is a summary of the Public Assessment Report (PAR) for Buspirone Hydrochloride 5 mg, 10 mg, 15 mg and 30 mg Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Buspirone Hydrochloride Tablets in this lay summary for ease of reading.

For practical information about using Buspirone Hydrochloride Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Buspirone Hydrochloride Tablets and what are they used for?
These applications are for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the UK/European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Buspirone Hydrochloride may be used for the:
- short term management of anxiety disorders
- relief of symptoms of anxiety with or without symptoms of depression

How do Buspirone Hydrochloride Tablets work?
Buspirone tablets belong to a group of medicines called anxiolytics. These medicines work on the central nervous system, altering levels of chemicals in the brain.

How are Buspirone Hydrochloride Tablets used?
The pharmaceutical form of these medicines is a tablet, and the route of administration is oral (by mouth).

The tablets should be swallowed with water, at the same time each day. Buspirone Hydrochloride Tablets should be taken consistently with or without food.

Doses:
Adults (including the elderly)
The usual starting dose is 5 mg two to three times a day, which may be increased every two to three days. The usual dose the patient will be maintained on is 15 mg to 30 mg a day in divided doses. The maximum daily dosage should not exceed 60 mg per day.
Use in Children and Adolescents
Buspirone Hydrochloride Tablets are not recommended for use in children or adolescents under the age of 18.
Patients with liver or kidney problems – If the patient has liver or kidney problems, the doctor may prescribe a lower dose.

For further information on how Buspirone Hydrochloride Tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Buspirone Hydrochloride Tablets have been shown in studies?
As the active substance buspirone hydrochloride has been in clinical use for over 10 years, data were provided in the form of literature references to show that Buspirone Hydrochloride Tablets is a safe and efficacious treatment for short-term management of anxiety disorders and the relief of symptoms of anxiety with or without accompanying symptoms of depression

What are the possible side effects of Buspirone Hydrochloride Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Buspirone Hydrochloride Tablets (which may affect more than 1 in 10 people) are dizziness, headache, and sleepiness.

Why were Buspirone Hydrochloride Tablets approved?
It was concluded that the data provided from literature references had shown that Buspirone Hydrochloride Tablets is effective in the treatment of short-term management of anxiety disorders and the relief of symptoms of anxiety with or without accompanying symptoms of depression. Furthermore, the well-established use of the active substance buspirone hydrochloride has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Buspirone Hydrochloride Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Buspirone Hydrochloride Tablets is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

The RMP details the important risks of Buspirone Hydrochloride Tablets, how these risks can be minimised, any uncertainties about Buspirone Hydrochloride Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Buspirone Hydrochloride Tablets:

Summary of safety concerns	
Important identified risks	• Drug interaction with seratonergic drugs including monoamine oxidase inhibitor (MAOI) • Use of buspirone in severe renally or hepatically impaired patients. • Use of buspirone in patients with acute narrow-angle glaucoma • Use of buspirone in patients with myasthenia gravis • Use of buspirone in patients with drug dependence • Use of buspirone in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption • Drug interaction with erythromycin • Drug interaction with itraconazole • Depression • Confusional state
Important potential risks	• Drug interaction leading to decrease in levels of buspirone • Drug interaction leading to increase in levels of buspirone • Increase in prothrombin time due to concomitant use of buspirone and warfarin
Missing information	• Long-term use in individuals below 18 years of age • Use in pregnancy and lactation • Long term toxicity

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Buspirone Hydrochloride Tablets

Marketing Authorisations for Buspirone Hydrochloride Tablets were granted in the United Kingdom (UK) on 28 July 2021.

The full PAR for Buspirone Hydrochloride Tablets follows this summary.

This summary was last updated in December 2025.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Buspirone Hydrochloride 5 mg, 10 mg, 15 mg and 30 mg Tablets (PL 42289/0017-0020) could be approved.

The products are approved for the following indications:

for the treatment of short-term management of anxiety disorders and the relief of symptoms of anxiety with or without accompanying symptoms of depression.

The name of the active substance is buspirone hydrochloride which belongs to the pharmacotherapeutic group of anxiolytics, azaspirodecanedione derivatives.

Buspirone is a member of the azapirone class of drugs. It has anxiolytic activity but is largely lacking in sedative and muscle relaxant effects and anticonvulsant activity.

Its mechanism of action has yet to be fully explained. Evidence to date suggests that its activity is based on its effects on serotonin (5-HT) receptors. It acts as an agonist of presynaptic and partial agonist of post-synaptic 5-HT1A subtype receptors. It is thought this initiate long-term changes in central 5-HT neurotransmission, producing the efficacy seen in the treatment of anxiety. Buspirone is thought to have antagonist activity at D2 receptors at the doses stipulated for anxious disorders, though it is unclear if this is linked to its anxiolytic activity.

Buspirone's effects on GABAergic mechanisms are unclear. It does not directly interact with either the benzodiazepine-GABA receptor complex or GABA receptors. However, there is indirect evidence for buspirone having a GABA antagonist-like action.

There has been no evidence of pharmacodependence in studies performed in animals and on humans.

These applications were approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of this/these product(s).

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) 28 July 2021.

II QUALITY ASPECTS

II.1 Introduction

These products consist of tablets containing 5 mg, 10 mg, 15 mg and 30 mg of buspirone hydrochloride, respectively.

In addition to buspirone hydrochloride, these products also contain the excipients lactose, microcrystalline cellulose, sodium starch glycolate (Type B), magnesium stearate, and silica colloidal anhydrous.

The finished products are packaged in Alu-Alu Film/Aluminium (OPA-Al-PVC) blister pack. The tablets are packed in blisters containing 21, 30, 56, 60, 84 & 90 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

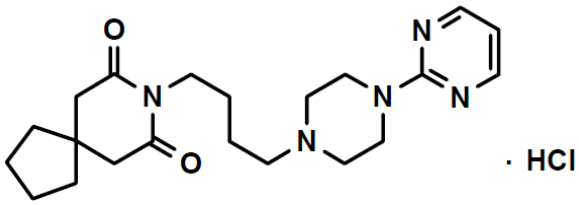
INN: buspirone hydrochloride

Chemical Name: 8-Azaspiro[4,5]decane-7,9-dione, 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-, monohydrochloride

N-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,1-cyclopentanediacetamide monohydrochloride

Molecular Formula: $C_{21}H_{31}N_5O_2$ HCl

Chemical Structure:



Molecular Weight: 421.96

Appearance: White crystalline powder

Solubility: USP: Very soluble in water; freely soluble in methanol and in methylene chloride; sparingly soluble in ethanol and in acetonitrile; very slightly soluble in ethyl acetate; practically insoluble in hexanes.

Ph. Eur.: Freely soluble in water and in methanol; practical insoluble in acetone

The information related to the active substance was provided in an ASMF. The Active substance is the subject of a Ph. Eur. monograph.

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

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

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT(S)

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose, no excipients of animal or human origin are used in the final products.
These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the product(s)

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

Satisfactory batch formulation data have been provided for the manufacture of the product(s), along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification(s)

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life 24 months, without special storage condition requirements, is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

These applications were submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as well-established use applications. No new non-clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology

As a non-benzodiazepine, buspirone is a psychotherapeutic agent for the treatment of anxiety. It exhibits both a non-traditional clinical profile and a unique spectrum of activity within the central nervous system.

Primary pharmacodynamics

Binding affinity

One study in rats reported the induction of conditioned place preference (a technique to evaluate preferences for environmental stimuli that have been associated with a positive or negative reward) following administration of 1 and 3 mg/kg (SC) buspirone. This is suggestive of an important role of 5-HT1A receptors in drug-induced sensitisation and locomotor activity.

Buspirone 1.0 mg/kg has been reported to decrease 5-HT turnover in the striatum without producing a significant decrease in motor activity. Furthermore, it has been suggested that the decreased availability of 5-HT at somatodendritic 5-HT1A receptors may produce an inhibitory influence on DA neurotransmission. Repeated administration of buspirone at a dose of 1 mg/kg decreased the responsiveness of somatodendritic 5-HT1A receptor responsiveness as buspirone-induced decreases of 5-HT metabolism were smaller in repeated buspirone treated animals.

Coadministration of buspirone (1 mg/kg) reversed apomorphine induced sensitisation. Moreover, repeated administration of buspirone at a dose of 2 mg/kg but not 1 mg/kg also elicited sensitisation in motor behaviour. Buspirone may oppose the development of sensitisation to apomorphine by decreasing the sensitivity of somatodendritic 5 HT1A receptors.

Buspirone has also been suggested to affect DA neurotransmission. An early report suggested that buspirone has a high affinity for the DA agonist (N-nnorpropylapomorphine) and a lower affinity for antagonist (spiperone) binding sites concluding that buspirone may act as a presynaptic DA agonist. However, it has since been confirmed that buspirone is without presynaptic agonist activity but does possess antagonist activity at the DA autoreceptors. In rats, striatal DA synthesis and metabolism were markedly increased following administration of buspirone, at an optimal dose of 3 mg/kg (SC) causing a 400% increase. However, it appears that buspirone may have another site of action in addition to the DA autoreceptor after it was shown that nigrostriatal DA impulse flow was enhanced following administration of buspirone even after a large dose of haloperidol (postsynaptic mesolimbic and striatal D2 and D1 DA receptor blocker) which served to block DA receptors.

Buspirone has been shown to act as an antagonist of D2 receptors, although its affinity is 15-fold weaker than for the 5HT1A receptors. Postsynaptically, buspirone does appear to weakly block DA receptors, although its effects are not what are typically expected. Buspirone up to 10 mg/kg cause hypoactivity but unlike the large doses of other postsynaptic DA receptor blockers, it did not result in catalepsy. Furthermore, buspirone is not effective as an antipsychotic at doses up to 2 mg/day, although it does inhibit, although weakly, stereotypies.

Therefore, buspirone must possess weak antagonism at the classical postsynaptic DA receptors due to the observed increase in DA cell impulse without producing stimulant-like behaviour (i.e. stereotypies). More recently, another rat study has investigated dose dependent effects of buspirone on DA neurotransmission. This study clearly showed that buspirone preferentially blocks the presynaptic rather than the postsynaptic D2 receptors. Buspirone doses at 1.25, 2.5 and 5.0 mg/kg blocks only presynaptic nigrostriatal D2 DA autoreceptors increasing synthesis and availability of DA. Only at larger doses of 10, 20 and 40 mg/kg are postsynaptic striatal D2 and D1 receptors successfully blocked.

The nucleus incertus (NI), a brainstem structure with diverse anatomical connections, is implicated in anxiety, arousal, hippocampal theta modulation, and stress responses. It expresses a variety of neurotransmitters, neuropeptides and receptors such as 5-HT1A, D2 and CRF1 receptors. The NI may play a role in the neuropharmacology of buspirone, a clinical anxiolytic which is a 5-HT1A receptor partial agonist and a D2 receptor antagonist. Several preclinical studies have reported a biphasic anxiety-modulating effect of buspirone but the precise mechanism and structures underlying this effect are not well-understood. Systemic buspirone (3 mg/kg) induced anxiogenic effects in elevated plus maze, light-dark box and open field exploration paradigms in rats and strongly activated the NI, as reflected by c-Fos expression. This anxiogenic effect was reproduced by direct infusion of buspirone (5 μg) into the NI, but was abolished in NI-CRF saporin- lesioned rats, indicating that the NI is present in neural circuits driving anxiogenic behaviour. Studies with NAD 299, a selective 5-HT1A antagonist, or quinpirole, a D2/D3 agonist, were conducted to examine the receptor system in the NI involved in this anxiogenic effect. Opposing the 5-HT1A agonism but not the D2 antagonism of buspirone in the NI attenuated the anxiogenic effects of systemic buspirone.

Mechanism of action

Biochemically, buspirone is unlike the benzodiazepines in that it neither stimulates nor inhibits 3H-benzodiazepine binding, does not affect the influence of GABA or halide anion on 3H-benzodiazepine binding, and does not interfere with GABA binding or uptake. Buspirone lacks anticonvulsant activity, interacts minimally with CNS depressants, and does not cause muscle relaxation. Its tranquilizing activity is characterized by the ability to (1) tame aggressive rhesus monkeys, (2) block conditioned avoidance responding in the rat, (3) inhibit shock-induced fighting in the mouse, and (4) attenuate shock-induced suppression of drinking in the rat. In vitro binding experiments indicate that buspirone lacks significant activity at several binding sites. It appears to interact only with the dopaminergic system and possesses properties that are similar to both dopamine agonists and dopamine antagonists.

The mechanism of action of buspirone is explained by an effect on the 5-HT system. The main source of 5-HT in the forebrain is the dorsal raphe nucleus (DRN). Acute and chronic buspirone treatments in rats significantly lowered the mean optical density of nNOS in the DRN as compared to controls. Meanwhile only the chronic buspirone treatment reduced the mean density of 5-HT and TH immunoreactivity but not the acute buspirone as compared to saline treated animals.

Buspirone caused inhibition of firing of these neurons when given IV (ED_{50} = 0.011 mg/kg), IP (ED_{50} = 0.088 mg/kg), and IG (effective dose = 1.0-20.0 mg/kg). Buspirone also inhibited these cells when it was administered to the outside of recorded neurons by microiontophoresis (effective currents =2-15 nA). Iontophoretically applied buspirone did not potentiate nor block the effects of iontophoretically applied GABA. Systemic administration

of two putative buspirone metabolites (1,2-pyrimidinyl piperazine and 5-hydroxy buspirone) in relatively high doses had a weak effect and no effect, respectively, on dorsal raphe neuronal firing. It is concluded that buspirone potently and directly inhibits the firing of serotonergic dorsal raphe neurons in the rat. Since buspirone inhibits the firing of serotonergic dorsal raphe neurons and binds to 5- HT1A receptors, the study supported the notion that central serotonergic systems may be involved in the therapeutic effects of anxiolytic drugs.

Buspirone 0.1 mg/kg were administered subcutaneously 15 min before testing, significantly increased black-white transitions (BWT) in control rats but had no effect in animals injected intracerebroventricularly one week before with 150 µg 5,7-dihydroxytryptamine (in 20 µL). Infusion of buspirone in the median raphe (but not in the dorsal raphe) significantly enhanced BWT, at doses from 1 µg to 10 µg (in 0.5 µL). Buspirone 5 and 10 µg, but not 1 µg, administered in the median raphe, significantly enhanced motor activity of rats during the first 10 min of testing in the activity cages. The effect on BWT of 5 µg buspirone in the median raphe was completely antagonized in animals which had received either 5,7-dihydroxytryptamine intraventricularly, 150 µg (in 20 µL), one week before or an infusion of 0.1 µg (in 0.5 µL) (-)-propranolol in the same area 5 min before. (-)-Propranolol infused in the median raphe did not modify the effect of buspirone on locomotion. Infusion of 5 µg buspirone (in 0.5 µL) in the median raphe significantly enhanced punished responses in a conflict test with no effect on unpunished responding. Buspirone infused in the dorsal raphe had no effect on punished or unpunished responding over a wide dose range. The results indicate that at the relatively low dose used in the present study buspirone produces an anxiolytic effect by acting on central 5-hydroxytryptaminergic neurones. It is likely that activation of 5-hydroxytryptamine1A-receptors in the median raphe is involved.

Buspirone at the dose of 0.5 and 1.5 mg/kg IP given before test session, which was 24 h after the aversive training, significantly decreased freezing response within a limited dose range of the U-shaped dose-response relationship. Exposure of animals to aversively conditioned context (a contextual fear) induced the production of c-Fos protein in the dentate gyrus, CA-1 and CA-3 layers of the hippocampus. Pre-treatment with buspirone (1.5 mg/kg) significantly attenuated the effects of aversive memory on c-Fos protein expression in the CA-1 and CA-3 layers of the hippocampus. These immunocytochemical results support previous data obtained in our laboratory with the help of selective neurotoxic lesions and intrahippocampal drug injections suggesting an important role of hippocampus in the anxiolytic effects of buspirone.

Pharmacological studies with NAD 299, a selective 5-HT1A antagonist, or quinpirole, a D2/D3 agonist, were conducted to examine the receptor system in the NI involved in this anxiogenic effect. Opposing the 5-HT1A agonism but not the D2 antagonism of buspirone in the NI attenuated the anxiogenic effects of systemic buspirone. In conclusion, 5-HT1A receptors in the NI contribute to the anxiogenic effect of an acute high dose of buspirone in rats and may be functionally relevant to physiological anxiety.

The effects of buspirone (0.5 mg/kg) on the neuroendocrine and serotonergic responses to stress were monitored in rats. Exposure to 2-h of restraint stress increased circulating levels of corticosterone, noradrenaline and glucose. The metabolism of 5-hydroxytryptamine (5-HT; serotonin) increased in the brain. Prior administration of buspirone did not alter levels of corticosterone, noradrenaline and glucose in unrestrained rats, but inhibited stress-induced increase in the activity of hypothalamic-pituitary-adrenal (HPA) axis and circulating levels of glucose. Restraint-induced rise in brain 5-HT and 5-hydroxyindole-acetic acid (5-HIAA) was

also attenuated by buspirone. Unrestrained animals injected with buspirone also exhibited a decrease in brain 5-HIAA concentration. The findings are discussed in the context of the role of somatodendritic 5-HT(1A) receptors in responses to stress.

Anti-anxiety-antidepressant effects of buspirone

Twenty-eight albino Wistar rats were tested in two different arena settings, an enclosed (low anxiety) and an exposed open field (high anxiety). Half received a 1 ml saline injection while the others received buspirone 3 mg/kg. The data showed clear differences in the two open-field settings, suggesting a higher anxiety level in the exposed open field. Buspirone treatment reduced the behavioural activity in both the enclosed and exposed open-field, which is generally interpreted as an anxiogenic effect. However, buspirone increased the time in the centre areas and decreased the frequencies in the outer regions. These behavioural changes are generally seen as an anxiolytic effect. Correlation analysis showed that buspirone treatment disrupted the relation between indices of anxiety. The reduced activity and increase in time spent in the centre areas are indicative of both an anxiogenic and an anxiolytic effect, respectively.

Ipsapirone and buspirone administered in single doses (5-20 mg/kg) did not affect the immobility time in the rat forced swimming test. When administered in the same doses in a three-injection course in 24 h, buspirone was also inactive, while ipsapirone slightly but significantly reduced the immobility time only after a dose of 5 mg/kg. On the other hand, gepirone administered both in single doses (2.5-20 mg/kg) and in a three-injection course (5-20 mg/kg) potently and dose-dependently shortened the immobility time. 1-(2-Pyrimidinyl)-piperazine (1-PP; 5-20 mg/kg), a common metabolite of all the three drugs, administered in single doses or in a three-injection course, was inactive in the forced swimming test. In rats pre-treated with proadifen (50 mg/kg), a non-selective drug metabolism inhibitor, both ipsapirone and buspirone administered in single doses (5-20 mg/kg) reduced the immobility time in a dose-dependent manner. Proadifen also potentiated the anti-immobility effect of gepirone (5 and 10 mg/kg). The anti-immobility effect of single doses (20 mg/kg) of ipsapirone, buspirone and gepirone in proadifen-pre-treated animals was completely abolished by 1-PP (4 mg/kg). These results indicate that the antidepressant-like activity of the examined drugs in the behavioural despair test is masked (ipsapirone, buspirone) or attenuated (gepirone) by their metabolite 1-PP.Pulse voltammetry was used in rats in association with chronically implanted carbon fibre microelectrodes to record 5HIAA, the serotonin metabolite in the extracellular space, almost continuously. Buspirone, 2.5 mg/kg IP was ineffective, but the dose of 10 mg/kg lowered 5HIAA between about 45 and 150 min; the same decrease was obtained with 40 mg/kg. This effect can be explained by an agonistic action on 5HT1A receptors. The metabolite 1PP, which displays alpha 2 adrenoceptor blocking properties, either had no effect or raised extracellular 5HIAA, depending on the dose (1.5 or 6 mg/kg). The rapid metabolization of buspirone to 1PP can thus explain the short time course of the drug effect. Pre-treatment with 1PP could only partially prevent buspirone's effect on the serotoninergic system.

In the communication box experiments, non-foot-shocked mice (responder) exposed to the emotional responses of foot-shocked mice (sender), 3 hr per day for 3 days, developed gastric lesions. Single treatments of diazepam (1, 2, 5 mg/kg) and SC-48274 (novel anxiolytic, 25, 50 mg/kg) prevented gastric lesion formation, but buspirone at 2.5-10 mg/kg did not. A 3-day treatment with SC-48274 at doses over 5 mg/kg prevented gastric lesions; and a 3-day treatment with buspirone at 2, 5 and 10 mg/kg prevented the lesions with a U-shaped dose-response. Diazepam also prevented gastric lesion formation at the doses of 1 and 2 mg/kg. In the passive avoidance response study, the step-down latency for rats to enter from the

illuminated compartment to the dark one was recorded. Single treatments of SC-48274 (25 mg/kg), diazepam (5, 10 mg/kg) or buspirone (25 mg/kg) shortened the delayed latency. These results suggest that SC-48274 has anxiolytic activity of the same potency as buspirone and repeated-dose administration is needed to induce anxiolytic activity.

Small platform stress for 24 hours increased the locomotor activity of mice and induced anxiolytic-like effect in the plus-maze and hole-board tests. Administration of buspirone either did not affect (2.0 and 4.0 mg/kg) or inhibited (8.0 mg/kg) locomotion in control animals. The inhibition of locomotor activity by buspirone was greater in small platform stressed mice. In control mice buspirone in doses 2.0 and 4.0 mg/kg exerted anxiolytic effect in the plus-maze and hole board test that was reflected by an increase in the percentage of entries onto and the percentage of time spent on the open arms of the plus-maze and increased number of head-dippings in the hole-board test. In contrast, in small platform stressed mice, buspirone did not induce anxiolytic action in the plus-maze and hole-board tests at any dose tested. In doses 2.0 and 4.0 mg/kg buspirone produced a sedative effect that was reflected by a decrease in the total number of entries made onto the open and into the closed arms of the plus-maze and a decrease in the number of head-dippings and rearings in the hole-board test. These data suggest that small platform stress induces a sensitization of mice to the motor depressant effect of buspirone. At the same time small platform stress induces hyposensitivity to the anxiolytic effect of buspirone.

Different classes of antidepressants [imipramine (tricyclic), maprotiline (noradrenline reuptake inhibitor), venlafaxine (mixed serotonin and noradrenaline reuptake inhibitors), fluvoxamine and sertraline (selective serotonin reuptake inhibitor)] were tested in the same randomised experimental session, alone and in combination with 5-HT1A and 5-HT1B receptor agonists [buspirone (partial 5-HT1A agonist), anpirtoline (5-HT1B agonist)] in the mouse forced swimming test. All antidepressants were found to be active in the mouse forced swimming test in 4-week-old mice and 40-week-old mice, with the exception of fluvoxamine in the 40-
week-old mice. The anti-immobility effect after antidepressant administration was higher in 4- week-old male mice than in 40-week-old male mice. Venlafaxine is the most active antidepressant drug in 40-week-old mice. Prior administration of buspirone (0.06 mg/kg, IP.) or anpirtoline (1 mg/kg, IP) enhanced the antidepressant-like effects in 4-week-old mice (except in the case of sertraline, 8 mg/kg). In elderly mice, only prior administration of buspirone enhanced the antidepressant-like effects of fluvoxamine.

Stressed (ST) and unstressed (UST) mice were evaluated in the exploratory behaviour test (EBT) or burying behaviour test (BBT). In addition, the action of increasing doses of the 5-HT(1A) compounds buspirone, 8-OH-DPAT and indorenate in ST and UST mice was analyzed using the EBT. A spontaneous ambulatory behaviour test was carried out immediately after the anxiety tests. One session of forced swimming (FS) induced anxiolytic-like behaviour in mice tested in both the EBT and the BBT. This effect of FS was blocked by a previous administration of either picrotoxin or WAY 100635. The 5-HT(1A) compounds produced a clear anxiolytic-like effect in UST animals. By contrast, with low doses of either 8-OH-DPAT (0.01 mg/kg), buspirone (0.03 mg/kg) or indorenate (0.3, 0.6 mg/kg) ST mice showed a decrease in the anti-anxiety-like effect observed after FS. No change in ambulation that could mask the results of the anxiety test was registered.
Female rats were exposed to alternate days of isolation and moderate crowding for 2 weeks. Group composition was changed for each crowding phase. Basal anxiety and the anxiolytic efficacy of buspirone were assessed by the social interaction test of anxiety 24 h after the last crowding phase. Crowding appeared stressful, as it increased plasma glucocorticoid levels in

less than 1 h. Anxiety-like behaviours were increased by social instability compared with stable group housing. In group housed controls, buspirone markedly suppressed locomotion, without clear effects on anxiety-related behaviours. Social instability attenuated the locomotor suppressive effects of buspirone but made the anxiolytic effects of the compound more conspicuous. The effects of individual housing (assessed earlier) and social instability (assessed here) on buspirone efficacy appear qualitatively different. Buspirone abolishes stress-induced anxiety but has no anxiolytic effects in controls.

The effects of acute serotonin (5-HT) 5-HT1A receptor agonist buspirone (0.5, 1.0, 2.5 and 5.0 mg/kg, SC), gepirone (5.0 and 10 mg/kg, SC), and 8-OH-DPAT (0.1, 0.25, and 0.5 mg/kg, IP) were studied treatment on the apomorphine-induced aggressive behaviour in adult male Wistar rats. Buspirone in doses of 2.5 and 5.0 mg/kg completely blocked, gepirone (10 mg/kg) significantly attenuated the aggressiveness, and 8-OH-DPAT abolished aggressive behaviour only in the lowest dose used (0.1 mg/kg) which effect disappeared in higher doses. The anti-aggressive effect of buspirone (2.5 mg/kg) and gepirone (10 mg/kg) was not reversed by a 5-HT1A receptor antagonist WAY 100635 (0.3 mg/kg). All 5-HT1A receptor agonists tested dose-dependently decreased the exploratory behaviour of experimentally naive rats, while buspirone (2.5 mg/kg) and gepirone (10 mg/kg) had only a weak effect on the locomotor activity and stereotyped behaviour in the apomorphine-presensitised rats. 5-HTIA receptors may be involved in the mediation of the apomorphine-induced aggressive behaviour in adult male Wistar rats. However, the prominent anti-aggressive effect of buspirone, and to a lesser extent--gepirone, seems to be mediated by some other mechanisms, evidently via the dopamine D2 receptors.

The effects of buspirone, a nonselective (diazepam), and a selective (zolpidem) GABA(A) receptor agonist were compared in the open field test of neophobia. Unhabituated rats were pre-treated with the drugs once, prior to a first exposure to the open field, and their behaviour was recorded both during this test and during a second trial 24 h later. It has been hypothesized that the decrease in exploratory activity observed during the second test session may be considered an adaptive reaction to the first day aversive experience (neophobia). If so, a selective modulation of 5-HT and GABA systems activity during the test could bring about significant changes in animal behaviour on the retest. Buspirone at the lowest dose of 0.3 mg/kg revealed anxiolytic-like properties on the first day, whereas the action of diazepam and zolpidem was modulated by the dose-related sedative effect. At the dose of 2.4 mg/kg buspirone elicited delayed in time anxiolytic-like action, i.e., produced the anti-thigmotactic effect during the retrial 24 h later. Diazepam and zolpidem failed to exhibit similar profile of action. Autoradiography of [^{3}H]muscimol binding after pretreatment of rats with buspirone showed a significant increase in the selective radioligand binding within the frontal cortex and a similar, near-significant tendency in the dentate gyrus of the hippocampus. The behavioural data validate buspirone as important drug for the treatment of anxiety disorders, devoid of disruptive influence on motor and cognitive processes.

The anxiolytic-like activity of alnespirone and buspirone, two 5-HT(1A) receptor agonists, were studied in a modified Geller-Seifter conflict model, and examined the role of 5-HT(1A) receptors by studying whether WAY-100635, a selective antagonist at these receptors, blocked their effects. Administered s.c. 30 minutes before testing, 0.5 and 1mg/kg alnespirone significantly increased punished responding, whereas lower doses (0.125 and 0.25 mg/kg) had no effect. At 1mg/kg, alnespirone significantly reduced the rates of unpunished responding. One dose of buspirone (1mg/kg) significantly increased punished responding and reduced unpunished responding. Lower doses were ineffective. Administered s.c. 40 minutes before testing, WAY-100635 had no effect on any parameter but completely

antagonized the effects of alnespirone (1mg/kg) and buspirone (1mg/kg) on punished responding. The ability of buspirone to reduce unpunished responding was not antagonized by WAY-100635, probably reflecting a sedative effect of buspirone due to dopamine D2 receptor blockade. The results suggest that alnespirone and buspirone have anxiolytic-like activity in a conflict procedure by stimulating 5-HT(1A) receptors, presumably at a presynaptic level.

The effect of prolonged administration of high doses of buspirone on its 5-HT release-inhibitory and anxiolytic-like properties was investigated. The 5-HT release inhibitory effect of a challenge dose of buspirone (0.5 mg/kg, s.c.) was identical in rats chronically treated with vehicle or buspirone (10 mg/kg, b.i.d. for 10 weeks), as estimated by in vivo microdialysis in the ventral hippocampus. In the same set of animals there was a significant anxiolytic-like effect in the elevated plus-maze after 5 weeks of treatment with buspirone. The results indicate that the functional capacity of 5-HT release-controlling 5- HT1A autoreceptors is retained upon chronic administration of buspirone, and that this effect may well be associated with the anxiolytic-like action of the compound.

The effects of acute and chronic administration of buspirone, a serotonin 5-HT1A agonist, on the 5-HT synthesis rates in various rat brain structures were investigated using alpha-[^{14}C]methyl-L-tryptophan (alpha-[^{14}C]MTrp) and an autoradiographic method. In the acute treatment study, buspirone (10 mg/kg) was injected subcutaneously 30 min before alpha-[^{14}C]MTrp administration (30 microCi over 2 min) into a femoral vein. In the chronic treatment study, buspirone was given in a sustained fashion (10 mg/kg/day) for 14 days using an osmotic minipump implanted subcutaneously. Rats were killed 60 and 150 min after alpha-[^{14}C]MTrp administration (two-time point method). A single dose of buspirone induced a significant decrease of 5-HT synthesis throughout the brain with the exception of the pineal body. However, the chronic treatment with buspirone did not induce significant differences in 5-HT synthesis in the brain. There was no significant difference in plasma free tryptophan concentration between any of the groups. The unaltered 5 HT synthesis rates in the chronic treatment study likely reflect a normalization of this parameter due to a desensitization of 5-
HT1A autoreceptors on the cell body of 5-HT neurons, which has been previously shown to occur following long-term treatment with 5-HT1A agonists.

The effects of buspirone were studied on an animal model of tardive dyskinesia, i.e., the quantification of orofacial dyskinesia in rats repeatedly treated with reserpine. Rats were cotreated with saline [SAL] or buspirone [BUS] (3.0 mg/kg IP BID) and vehicle [VEH] or reserpine [RES] (0.1 mg/kg SC once every other day) for 19 days. On the day 20, the animals were observed for quantification of the behavioral parameters of orofacial dyskinesia: tongue protrusion and vacuous chewing movements frequencies and duration of twitching of the facial musculature. Rats of the SAL + RES group exhibited a significant increase in the three behavioural parameters of orofacial dyskinesia relative to the rats of the SAL + VEH group. However, animals of the BUS + RES group showed only an increased frequency of vacuous chewing movements when compared to animals of the SAL + VEH
group. In addition, the duration of the facial twitching was significantly decreased in the BUS + RES group in relation to rats of the SAL + RES group. There were no significant differences in the orofacial parameters between the BUS + VEH and the SAL + VEH groups. Because it was also verified that chronic buspirone treatment was able to increase apomorphine-induced yawning behaviour, the possibility is raised that buspirone attenuates reserpine-induced orofacial dyskinesia through the development of dopamine autoreceptor supersensitivity.

Secondary pharmacodynamics

Antinociceptive properties

The pain-related effects of buspirone are mediated via the 5- HT1a Rs, specifically located within the ventrolateral medulla (VLM). The 5-HT1a R contribution in visceral pain transmission within the VLM is unclear. In anaesthetised rats, the colorectal distension (CRD) induced a significant increase in VLM neuron activity up to 201.5 ± 18.0% and depressor reactions up to 68 ± 1.8% of baseline. Buspirone (1-4 mg/kg IV) resulted in an inhibition of the CRD-induced neuron responses which were changed inversely with dose increase and decreased depressor reactions directly with dose increase. These effects were antagonized by intracerebroventricular WAY 100635. Buspirone exerts complex biphasic action on the pain related VLM neuron activity inversely depending on dose. The final effect of buspirone depends on the functional balance between of activation the pre- and postsynaptic 5-HT1a Rs in mediating pain control networks.

Buspirone, gepirone, and 8- OH-DPAT produced significant antinociception in a mouse hot-plate and abdominal constriction studies, which was prevented by atropine (5 mg/kg IP), the ACh depletor hemicholinium-3 (1 µg ICV), and the 5-HT1A antagonist NAN 190 (0.5 µg ICV) but not by naloxone (1 mg/kg IP), the $GABA_B$ antagonist CGP 35348 (100 mg/kg IP), and pertussis toxin (0.25 µg ICV). NAN 190 which totally antagonized buspirone, gepirone, and 8-OH-DPAT antinociception, did not modify the analgesic effect of morphine (5 mg/kg SC). In the antinociceptive dose range, none of the 5HT1A agonists impaired mouse performance evaluated by rota-rod and hole board tests. On the basis of these data, it can be postulated that buspirone, gepirone, and 8-OH-DPAT exert an antinociceptive effect mediated by a central amplification of cholinergic transmission.

Buspirone dose-dependently (0.1-1 mg/kg, IV antagonized mean arterial pressure change over a range of distensions (10-90 mmHg) in anaesthetised Wistar rats. In parallel studies conducted in awake animals, buspirone (1-5 mg/kg, SC) attenuated the abdominal withdrawal response, a nociceptive behaviour, in response to colorectal distension. This effect was antagonized by co-administration of the 5-HT(1A) receptor antagonist N-[2- [4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-2- pyridinylcyclohexane carboxamide (WAY-100635) (5 mg/kg, s.c.). It was concluded that buspirone exhibits significant visceral analgesic property in two models of abdominal nociception.

Effects of single and repeated administration of buspirone were monitored on pain threshold in the hot plate test and on spatial memory in the water maze test in rats. Effects on cumulative food intake were also monitored. The drug was administered intraperitoneally in doses of 0.1, 0.3, 1.0 and 2.0 mg/kg. Single and repeated administration of buspirone in doses of 0.1 mg/kg decreased pain threshold in the hot plate test, while doses of 1.0 and 2.0 mg/kg increased it. Effects of single and repeated administration were not different. A dose of 0.3 mg/kg had no effect. Food intake increased following single as well as repeated administration of 0.1 mg/kg buspirone; higher doses had no effect. Low doses (0.1 and 0.3 mg/kg) improved acquisition and retention of memory in the water maze test, while memory extinction was reduced. Higher doses had either no effect (1.0 mg/kg) or impaired (2.0 mg/kg) performance in this test. The results suggest potential therapeutic use of selected doses of buspirone as an analgesic and nootropic drug.

Antihypertensive properties

Sham-operated control and DOCA-treated hypertensive rats received buspirone (1 mg/kg/day p.o. for 4 weeks) and in the second set, in vivo and in vitro studies were carried out. In the case of in vivo studies, sham-operated control and DOCA-treated hypertensive rats received SB204741 or SB200646 (1 mg/kg/week i.v. for 4 weeks). Blood pressure was measured weekly by tail-cuff method. After completion of the treatment schedule, blood pressure and vascular reactivity to various agonists like 5-HT, noradrenaline and adrenaline were recorded. Chronic administration of buspirone, SB204741 and SB200646 produced a significant reduction in blood pressure and vascular reactivity to agonists in DOCA-salt hypertensive rats, implying an antihypertensive effect. However, chronic administration of the same drugs in sham control rats did not alter blood pressure and vascular reactivity to various agonists. For in vitro studies a similar treatment schedule was followed as in vivo studies and a cumulative concentration response curve of 5-HT was recorded on isolated thoracic aorta. Treatment with 5-HT2B antagonists shifted the concentration response curveof 5-HT to the right on isolated aorta. It was concluded that 5-HT1A agonist and 5-HT2B antagonists possess an antihypertensive effect.

Antiparkinsonism properties

Dopamine (DA) replacement therapy with l-DOPA remains the standard pharmacotherapy for Parkinson's disease (PD). Unfortunately, chronic l-DOPA treatment is accompanied by development of motor fluctuations and l-DOPA-induced dyskinesia (LID). While serotonin (5- HT)(1A) agonists acutely reduce these complications, their prophylactic and long-term effects are not well-delineated. To test this, male Sprague-Dawley rats received unilateral 6-hydroxydopamine (6-OHDA) lesions. In experiment 1, l-DOPA-primed rats were pre-treated with Vehicle (0.9% NaCl), various doses of the partial 5-HT(1A) agonist, buspirone (0.25, 1.0 or 2.5 mg/kg, ip) or buspirone (2.5 mg/kg, ip)+the 5-HT(1A) antagonist, WAY100635 (0.5 mg/kg, ip) 5 min prior to l-DOPA (12 mg/kg+15 mg/kg benserazide, ip). Rats were tested for LID using the abnormal involuntary movements (AIMs) scale and motor performance using the forepaw adjusting steps test (FAS). In experiment 2, l-DOPA-naïve rats received coadministration of l-DOPA+buspirone (1.0 or 2.5 mg/kg, ip) for 2 weeks. AIMs and FAS were measured throughout. In l-DOPA-primed rats, buspirone dose-dependently reduced LID and improved l-DOPA-related motor performance due to action at the 5-HT(1A) receptor. In l-DOPA-naïve rats, buspirone delayed LID development while improving l-DOPA's antiparkinsonian efficacy indicating the potential long-term benefits of 5-HT(1A) agonists for reduction of l-DOPA-related side effects.

The dopamine D3 receptor (DRD3) has been proposed as a target for drug development for the treatment of addictive disorders. Recently, the anxiolytic buspirone has been shown to have affinity for DRD3 and DRD4, and interest in repurposing it for addictive disorders has grown. Binding of [3H]-(+)-PHNO in the rat cerebellum and striatum was used to measure occupancy by buspirone of DRD3 or DRD2, respectively. Effects of buspirone in the rat gambling task (rGT) and the five-choice serial reaction time task (5-CSRTT) were examined. Buspirone occupied both the DRD2 and DRD3 at high doses and the DRD3, but not the DRD2, in the narrow dose range of 3 mg/kg. At 10 mg/kg, a disruption of performance on rGT was observed. All measures of performance on the rGT, except for perseverations, were affected at 3 mg/kg. On the 5-CSRTT, omissions were increased. Impairments in the rGT were not mimicked by the effects induced by satiation. Further, buspirone did not impair food-maintained responding under a progressive ratio schedule of reinforcement at any dose, suggesting that the effects of buspirone on the rGT cannot be explained by nonselective actions. Although buspirone had effects on the rGT at the dose that selectively occupied the DRD3, the effects found do not parallel those found in previous studies of the effects of selective.

A serotonin (5-HT)1A receptor partial agonist, buspirone, potentiates the clinical antidepressant properties of 5-HT reuptake inhibitors (SSRIs). Herein, we examined the interaction of buspirone with two SSRIs, duloxetine and fluoxetine, on extracellular levels of 5-HT, dopamine (DA), and noradrenaline (NAD) in single dialysate samples of freely moving rats. Duloxetine (5.0 mg/kg. s.c.) and fluoxetine (10.0 mg/kg, s.c.) increased dialysate levels of DA (65 and 60% vs. basal values, respectively). NAD (400 and 90%, respectively), and 5- HT (130 and 110%, respectively) in the frontal cortex (FCX). Buspirone (2.5 mg/kg, s.c.) similarly, elevated levels of DA (100%) and NAD (160%) but reduced those of 5-HT (-50%). Administered with buspirone, the ability of duloxetine and fluoxetine to increase 5-HT levels was transiently inhibited (over 60 min), although by the end of sampling (180 min) their actions were fully expressed. In contrast, buspirone markedly and synergistically facilitated the elevation in DA levels elicited by duloxetine (550%) and fluoxetine (240%). Furthermore, buspirone potentiated the induction of NAD levels by duloxetine (750%) and fluoxetine (350%). These data suggest that a reinforcement in the influence of SSRIs on DA and possibly. NAD but not 5-HT release in FCX may contribute to their increased antidepressant activity in the presence of buspirone. More generally, they support the hypothesis that a reinforcement in dopaminergic transmission in the FCX contributes to the actions of SSRIs and other antidepressant drugs.

Involvement of the serotonergic system in tail tremor induced by repeated administration of nicotine was investigated in rats. Tail tremor induced by nicotine (0.5 mg/kg, s.c.) was suppressed by a 5-HT(1A) receptor antagonist, N-2-[4-(2-methoxyphenyl)-1-piperazinyl-ethyl-N-(2-pyridinyl)cycloh exanecarboxamide trihydrochloride (WAY-100635; 0.3-3 mg/kg, IP), but not by a 5-HT(2) receptor antagonist, ketanserin (0.1-0.3 mg/kg, IP). The 5-HT(1A) receptor agonists, buspirone (1-20 mg/kg, i.p.), gepirone (1-10 mg/kg, i.p.), tandospirone (1- 10 mg/kg, i.p.) and (+/-)-8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT; 0.01-0.1 mg/kg, s.c.), enhanced the tail tremor. The enhancement of tail tremor by buspirone (10 mg/kg, i.p.) was blocked by WAY-100635 (0.3-3 mg/kg, i.p.). These findings suggest that nicotine induced tail tremor is mediated by 5-HT(1A) receptors and that 5-HT(1A) receptor antagonists are effective in the treatment of tremor.

In rat hippocampus after seizures and status epilepticus (SE) induced by pilocarpine there was a significant increase in lipid peroxidation and nitrite levels. However, no alteration was observed in superoxide dismutase and catalase activities. Buspirone pre-treatment produces significantly reduction of the lipid peroxidation level (60%) and nitrite content (44%) as well as increased the superoxide dismutase (47%) and catalase (40%) activities in rat hippocampus after seizures, when compared with the pilocarpine group. The IP injection of buspirone prior to pilocarpine suppressed the behavioural seizure occurrence. According to our results, the
oxidative stress is present during seizures. Buspirone exerted anticonvulsant effects associated with the inhibition of the development of oxidative stress. These results suggested a therapeutic use potential of buspirone in epilepsy treatment.

A study was aimed to determine the effect of low and high doses of buspirone on motor activity and striatal monoamine metabolism in rats. Behavioural and neurochemical effects of agents were monitored acutely. Motor activity was scored in open field. Neurochemical estimations in the striatum were carried out by high performance liquid chromatography. Administration of buspirone at low (1 mg/kg) and high (10 mg/kg) doses increased latency to move in open field and decreased number of squares crossed. The agent injected at a dose

of 1 mg/kg decreased dopamine concentration and increased the concentration of homovanillic acid. Increases of homovanillic acid were smaller at a dose of 1 mg/kg than 10 mg/kg. Changes in the levels of dihydroxyphenyl acetic acid were not significant. Administration of buspirone decreased 5-hydroxytryptamine metabolism at a dose of 1 mg/kg but not at a dose of 10 mg/kg. The results provided neurochemical evidence that low but not high dose of buspirone preferentially stimulates somatodendritic 5-hydroxytryptamine-1A
receptors resulting in a decrease in striatal serotonin metabolism. Low dose of buspirone could release dopaminergic neurons from inhibitory influence of serotonin and may be useful in reducing parkinsonian-like effects of traditional antipsychotics.

Anti-schizophrenic properties
Rats chronically treated with haloperidol exhibit vacuous chewing movements (VCMs) with the twitching of facial musculature and tongue protrusion, this is widely used as an animal model of TD. Evidence suggests a role of 5-hydroxytryptamine (5-HT; serotonin)-1A receptors in the pathogenesis and treatment of TD because repeated administration of haloperidol resulted in an increase in the effectiveness of 5-HT-1A receptors while drugs with agonist activity at 5-HT-1A receptors could attenuate haloperidol-induced VCMs. Rats treated with haloperidol at a dose of 1 mg/kg twice a day for 2 weeks displayed VCMs with twitching of facial musculature that increased in a time dependent manner as the treatment continued to 5 weeks. Coadministration of buspirone attenuated haloperidol-induced VCMs after 2 weeks and completely prevented it after 5 weeks. The intensity of 8-hydroxy-2-di (n-propylamino) tetralin (8-OH-DPAT)-induced locomotion was greater in saline+haloperidol injected animals but not in buspirone plus haloperidol injected animals. 8-OH-DPAT-induced decreases of 5-HT metabolism were greater in saline+haloperidol injected animals but not in buspirone+haloperidol injected animals. It is suggested that an impaired somatodendritic 5-HT-1A receptor dependent response is a major contributing factor in the pathophysiology of TD and a normalization of the somatodendritic response by drugs may help extending therapeutics in schizophrenia.

Safety pharmacology

Neurological effects
Diazepam and buspirone dose-dependently inhibited the expression of maternal aggression and the active components of maternal behaviour such as retrieving and nest building. 8-OH-DPAT did not affect these behaviours. 8- OH-DPAT (1.0 mg/kg) provoked the serotonergic syndrome and hypothermia; however,
ovariectomized animals showed more signs of the syndrome and a decrease in body temperature after 8-OH-DPAT than lactating rats. Buspirone, but not the other anxiolytics, reduced motor activity.

Renal effects
Buspirone, produces a dose-dependent biphasic effect on plasma renin activity in non-stressed rats. Low doses (0.1 - 2.0 mg/kg IP.) decrease while high doses (10.0 - 50.0 mg/kgIP) increase plasma renin activity. The maximal decrease in plasma renin activity was observed 30 minutes post-injection. In addition, buspirone (0.5 and 2.0 mg/kg i.p.) blocked the stress-induced rise in plasma renin activity.

Buspirone (3-100 mg/kg, p.o.) elicited increases in urinary volume and electrolyte excretion of conscious normotensive rats and decreased these parameters in conscious mice.

Intravenous and oral administration to anesthetized and conscious dogs elevated urinary volume and electrolyte excretion.

Cardiovascular effects
Administration of buspirone (0.5 mg/kg i.p.) produced a sustained reduction (15%) in heart rate but did not affect mean arterial pressure.

IV buspirone (0.3 or 3 mg/kg) in anesthetized rats elicited a transient pressor response (14 +/- 2 mmHg) and sustained bradycardia. However, oral administration (30 mg/kg) reduced the blood pressure and heart rate of conscious normotensive (-14 +/- 4 mmHg) and DOCA-salt hypertensive rats (-22 +/- 5 mmHg).

Buspirone was observed to possess alpha 1-adrenoceptor agonist activity in ganglion blocked anesthetized rats. Buspirone (0.3-3 mg/kg, i.v.) elicited transient elevations in the blood pressure of open-chest anesthetized dogs. There was a sustained increase in total peripheral resistance and a decrease in aortic blood flow, heart rate, right ventricular contractile force and left ventricular dp/dt max. Doses used to elicit the observed alterations in hemodynamic/renal function are considerably greater than those which produce anxiolytic effects.

In atenolol-pre-treated anaesthetised rabbits, buspirone (100 µg/kg IC) potentiated bradycardia and the changes in blood pressure and renal nerve activity. These effects could be attenuated by pre-treatment with the 5-HT(1A) receptor antagonist WAY-100635 (100 µg/kg IV) which alone had no effect on these reflex-evoked changes. However, WAY-100635 (100 µg/kg IC) did attenuate these reflex-evoked responses produced by activation of cardiopulmonary and aortic baroreceptors but not that caused by stimulation of chemoreceptors. When given IV buspirone was less effective in modulating the responses evoked by these three reflexes.

A study was aimed to determine whether 5-HT1A receptor-mediated pressor responses in hypovolemic animals are due to sympathoexcitation and/or direct vasoconstriction, blood pressure (BP), heart rate (HR), and renal sympathetic nerve activity (RSNA) responses to the partial 5-HT1A receptor agonist buspirone or the more selective, full 5-HT1A receptor agonist (+)-8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) were compared in intact and ganglionic blocked, hemorrhaged Sprague-Dawley rats.

Buspirone produced dose-dependent increases in BP, heart rate and renal sympathetic nerve activity in rats.
Ganglionic blockade with hexamethonium chloride blocked the pressor effect of 9.9 µg/kg 8-OH-DPAT and attenuated, but did not block, the pressor response to 0.2 mg/kg buspirone. In subsequent tests, rats treated with the selective alpha1-adrenergic receptor antagonist prazosin (25 µg/kg) continued to show extensive tachycardic and sympathoexcitatory responses to 0.2 mg/kg buspirone. Ganglionic blockade combined with prazosin completely blocked all responses to buspirone. Buspirone (0.2 mg/kg) produced significant bradycardic and sympathoinhibitory responses in euvolemic rats 3 min after injection. It is concluded that the pressor effect of buspirone is unique to hypovolemic animals and is mediated by sympathetic activation as well as direct activation of vascular alpha1-adrenergic receptors.

Metabolic effects
Buspirone did not affect plasma glucose levels of non-fasted mice, while it increased serum insulin levels. In fasted mice, buspirone significantly reduced glucose-induced

hyperglycemia and enhanced insulin release elicited by glucose. The major metabolite of buspirone, 1-(2-pyrimidinyl) piperazine (1- PP) increased serum insulin levels and induced a slight hypoglycemia in non-fasted mice. 1-PP decreases glucose-induced hyperglycemia and amplifies insulin release elicited by glucose in fasted mice. Since buspirone is mainly metabolized to 1-PP and formation of 1-PP occurs quickly, the inhibitory effect of buspirone on glucose-induced hyperglycemia is likely mediated by 1-PP.

Abuse, dependence and withdrawal
Rats were administered placebo, or 100 mg/kg diazepam, or buspirone for 21 days. Animals then received drug as well as a benzodiazepine antagonist RO-15-1788 15 mg/kg, or had the agent discontinued abruptly.
Buspirone-treated rats significantly gained weight when the drug was either abruptly ceased or given with RO-15-1 788. In contrast, significant weight loss was seen in diazepam-treated rats when the agent was given
RO-15-1788 or abruptly discontinued.

In rat models, buspirone was equivalent to saline when compared to oxazepam and pentobarbital in drug-discrimination tests, did not produce withdrawal signs after long-term use, and was an ineffective substitute for barbiturates after extended treatment.

Pharmacodynamic drug interactions

Sprague-Dawley rats responded for food under a fixed-ratio 10 schedule; afterward they were immediately placed on a 52°C hot plate. Morphine, baclofen, and buspirone were examined alone and in 1:1 combinations, based upon ED_{50} values. Morphine and baclofen effects were evaluated with the opioid antagonist naltrexone and the $GABA_B$ antagonist (3-Aminopropyl) (diethoxymethyl)phosphinic acid (CGP35348), respectively. Morphine, baclofen, and buspirone dose dependently decreased operant responding, with the calculated ED_{50} values being 7.09, 3.42, and 0.57 mg/kg, respectively. The respective antinociception ED_{50} values were 16.15, 8.75, and 2.20 mg/kg. Analysis of 1:1 combinations showed the effects of morphine plus baclofen to decrease schedule-controlled responding and to produce thermal antinociception were synergistic. Effects of morphine plus buspirone and baclofen plus buspirone to decrease schedule-controlled responding were additive. Effects of the two combinations to produce thermal antinociception were synergistic.

The influence of citalopram (20 mg/kg i.p.) and buspirone (3 mg/kg i.p.) on analgesic effects of morphine (10 mg/kg i.p.), metamizole (500 mg/kg i.p.) and indomethacin (10 mg/kg) was studied with tail-flick and hot-plate tests on mice. The results indicate that citalopram and buspirone decrease analgesic effects of morphine, metamizole and indomethacin. This mode of action is more pronounced in case of a single dose than after multiple doses.

In tests of anxiety in mice, it was found that paroxetine resulted in an anxiolytic-like effect at doses that did not modify motor performance. In the light/dark paradigm, buspirone significantly potentiated paroxetine, while in the four plates only one dose of buspirone (a 5HT(1A) partial agonist) increased the anxiolytic-like effect of paroxetine. Prior administration of 1-PP was without effect in the light/dark paradigm but antagonized the effect of paroxetine in the FPT.

Coadministration of buspirone with PCT attenuated the antinociceptive activity of PCT, whereas fluoxetine + PCT increased pain threshold in the hot-plate and formalin test.

Analgesic effect of PCT was not affected by ondansetron in formalin models. It attenuated analgesic action of PCT in hot-plate test.

III.3 Pharmacokinetics

Absorption

After oral administration of pharmacologically effective doses of buspirone hydrochloride to rats, the metabolite appears in significant amounts in body fluids and tissues; it is highly concentrated in the central nervous system, the brain-to-plasma concentration ratios being approximately 5 at the time of the C_{max}. In man given the anxiolytic dose of buspirone hydrochloride the metabolite (PmP) reaches higher plasma C_{max} values than its parent drug. Its plasma elimination t1/2 is more than double that for buspirone hydrochloride.

Pharmacokinetics of buspirone and its active metabolite, 1-pyrimidinyl piperazine (1-PP) following oral administration were assessed in rhesus monkeys at doses used in chronic toxicology studies. Inter-animal variability in the pharmacokinetics of buspirone was high. Examination of C_{min} vs time plots revealed that the steady state was attained by day 7 except for one monkey who demonstrated much higher C_{min} values. For buspirone, dose proportionality was concluded for both C_{max} and AUC on day 1 but not on day 7. The accumulation factor on day 7 for buspirone was nearly 5 for C_{max} and 7 for AUC when compared with day 1.
For 1-PP, dose proportionality was concluded except for C_{max} in male monkeys on day 7. In contrast to buspirone, 1-PP showed less than 2-fold accumulation in C_{max} and AUC values on day 7 compared with those on day 1. Exposure at a dose of 25 mg/kg once daily was in between the 12.5 mg/kg and 25 mg/kg twice-a-day regimens.

Cats received a single dose of amitriptyline (5 mg) and buspirone (2.5 mg) by the transdermal and oral route of administration with at least a 2-week washout interval between drug treatments. Systemic absorption of amitriptyline and buspirone administered by the transdermal route was poor compared with the oral route of administration.

After IV dosing in rats, plasma levels of buspirone declined in a multi-exponential manner with a terminal half-life of 78.0–111 min. The mean values for CL and Vss were observed to be high (97.9 mL/min/kg and 6220 mL/kg, respectively), indicating an extensive tissue distribution and rapid elimination of buspirone. The CL value of buspirone exceeded the rat hepatic blood flow rate (i.e., 50–80 mL/min/kg), suggesting that a considerable fraction of buspirone may be eliminated via extra-hepatic routes including the intestine and kidney in rats. After oral dosing, the plasma levels of buspirone increased within a very short time period (5–10 min) and then they decreased in a multi-exponential manner. The terminal half-life values (t 1/2) of buspirone in the oral study were not significantly different (p=0.144) from those in the intravenous study, indicating that buspirone given orally to rats does not exhibit flip-flop kinetics. The absolute oral bioavailability (F) was observed to be 17.5%. These results suggest that the systemic absorption of oral buspirone is rapid and incomplete in rats.

In rhesus monkeys buspirone hydrochloride solution was administered in a randomized manner by oral gavage at doses (expressed as buspirone free base) of 12.5, 25 and 50 mg/kg once a day on days 1 and 7 and twice a day on days 2±6. In the last period, all monkeys received 25 mg/kg buspirone as a single daily dose for 7 days. Pharmacokinetics of buspirone was dose-linear but not proportional for both C_{max} and AUC on day 7. The accumulation ratios for buspirone on day 7 were approximately 5 for C_{max} and 7 for AUC_{TAU}. Terminal elimination half-life ranged from less than 1 h to 23 h. The long t1/2 is most probably a

reflection of lack of adequate data points in the terminal elimination phase. Exposure of buspirone at the 25 mg/kg once-daily dose was generally in between that at the 12.5mg/kg twice-daily and 25 mg/kg twice-daily dose levels.

Plasma clearance (47.3 ± 3.5 ml/min/kg), volume of distribution (2.6 ± 0.3 l/kg), and half-life (1.2 ± 0.2 h) of 6-OH-buspirone in rats were similar to those for buspirone. Bioavailability was higher for 6-OH-buspirone (19%) compared with that for buspirone (1.4%). After IV infusions to steady-state levels in plasma, 6-OH-buspirone and buspirone increased 5-hydroxytryptamine (HT)(1A) receptor occupancy in a concentration-dependent manner with EC_{50} values of 1.0 ± 0.3 and 0.38 ± 0.06 microM in the dorsal raphe and 4.0 ± 0.6 and 1.5 ± 0.3 microM in the hippocampus, respectively. Both compounds appeared to be approximately 4-fold more potent in occupying presynaptic 5-HT(1A) receptors in the dorsal raphe than the postsynaptic receptors in the hippocampus. Oral dosing of buspirone in rats resulted in exposures (area under the concentration-time profile) of 6-OH-buspirone and 1-(2-pyrimidinyl)-piperazine (1-PP), another major metabolite of buspirone, that were approximately 12 (6-OH-buspirone)- and 49 (1-PP)-fold higher than the exposure of the parent compound.

Distribution

Buspirone is found in higher concentrations in the lung, kidney and fat than 'in muscle, heart, liver, brain and plasma. Concentrations of buspirone were 2 to 4 times higher in the brain than in plasma following an oral dose of 25 mg/kg, or an intravenous dose of 10 mg/kg. Buspirone is about 75% bound to plasma proteins in rats but was shown to be > 95% bound to human plasma proteins in vitro.

Highest densities of [3H]buspirone binding were localized in the caudate/putamen, nucleus accumbens septi, olfactory tubercle and in the glomerula of the olfactory bulb. This distribution pattern is different from any serotonin receptor but fits well with that of dopamine receptors.

(^{3}H)Buspirone binds with high affinity (KD = 11 nM) to sections from rat striatum. The regional distribution of (^{3}H)buspirone binding in rat and marmoset brain is characterized by high silver grain densities in the olfactory tubercle, nucleus accumbens and striatum. In the hypophysis, the pars intermedia is strongly labeled. Within the hippocampal formation, slightly higher binding site densities are found in the dentate gyrus. The distribution pattern of binding sites in the dentate gyrus varies according to the species investigated.

Metabolism and excretion

1-(2-Pyrimidinyl)-piperazine (1-PP) is an active metabolite of several psychoactive drugs including buspirone. 1-PP is also the major metabolite in the human circulation and in rat brains following oral administration of buspirone. The formation of HO-1-PP followed a Michaelis-Menten kinetics with a K(m) of 171 microM and V(max) of 313 pmol/min x mg protein in HLMs. Collectively, these results indicate that polymorphic CYP2D6 is responsible for the conversion of 1-PP to HO-1-PP.

Following IV buspirone (5 or 15 mg/kg in 15 min) or 1-PP (10 mg/kg in 15 min), the time course of the concentrations in blood were determined in conjunction with the effect on body temperature. The pharmacokinetics of buspirone and 1-PP were analyzed based on a two-compartment model with metabolite

formation. Differences in the pharmacokinetics of buspirone and 1-PP were observed with values for clearance of 13.1 and 8.2 ml/min and for terminal elimination half-life of 25 and 79 min, respectively. At least 26% of the administered dose of buspirone was converted into 1- PP. Complex hypothermic effects versus time profiles were observed, which were successfully analyzed on the basis of a physiological indirect response model with set-point control. Both buspirone and 1-PP behaved as partial agonists relative to R-(+)-8-hydroxy-2-(di-n-propylamino) tetralin (R-8-OH-DPAT) with values of the intrinsic activity of 0.465 and 0.312, respectively. Differences in the potency were observed with values of 17.6 and 304 ng/ml for buspirone and 1-PP, respectively.

In rat liver microsomes and hepatocytes, five metabolites of buspirone were identified in the microsomal incubates and seven in the hepatocyte incubates. The major metabolites arose from aromatic hydroxylation at C-5, Ndealkylation of the butyl chain, and hydroxylation at C-6' and C-3' on the azaspirodecanedione moiety. Metabolism was NADPH-dependent and was completely inhibited by cytochrome P-450 inhibitors SKF-525A and metyrapone. Metabolites o formed in vitro were good predictors of the primary metabolites formed in vivo. Hepatocytes and phenobarbital-induced rat liver microsomes were better predictors of in vivo metabolism of buspirone than non-induced rat liver microsomes.

In the rat, addition to the already known metabolites 5-hydroxy-buspirone and 1-pyrimidinylpiperazine, seven major metabolites were unambiguously identified together with unchanged drug. Ten minor metabolites were partially characterized. Hydroxylation alpha to the glutaramidyl carbon at the 6'-position on the bicyclo ring system, hydroxylation on the pyrimidine aromatic ring, and N-dealkylation of the butyl side chain were observed as major routes of metabolism. Minor routes of metabolism observed were: 3'-hydroxylation on the bicyclo ring system and formation of the methylated catechol derivatives. The identified metabolites accounted for greater than 90% of the total metabolites excreted in the rat bile and urine samples.

Buspirone is well absorbed but is subject to first-pass metabolism. The mean systemic availability is approximately 4 percent. Buspirone is eliminated primarily by oxidative metabolism, which produces several hydroxylated metabolites, including 5-hydroxy-buspirone and 1-pyrimidinylpiperazine. The latter metabolite is from 1 to 20 percent as potent as buspirone in a variety of pharmacologic tests; 5-hydroxybuspirone is essentially inactive.

After i.v. injection (10 mg/kg) to rats, buspirone is rapidly cleared from blood with a t1/2 (beta) or 30 min. After the same dose is given orally, the drug is not detectable in blood or brain within the limits of sensitivity of the method. The metabolite 1-(2-pyrimidinyl)-piperazine (1- PP) has a longer t1/2 than buspirone. It is present to about the same extent in rat plasma and brain after either i.v. or p.o. buspirone. Unlike buspirone, 1-PP accumulates in the brain reaching concentrations between four-and five times those in plasma. Its brain AUC is higher than that of buspirone even when buspirone is given i.v.

In humans, the systemic exposure to buspirone increases linearly in relation to the oral dose. Food increases the bioavailability of buspirone by decreasing first-pass metabolism; absorption is not markedly altered. The pharmacokinetics of buspirone were not significantly different in men and women or in individuals 21 to 40 years old compared with those over 65 years of age. Half-life values observed in healthy volunteers ranged from two to 33 hours. Mean half-life values observed in healthy volunteers in the 14 studies conducted to date ranged from 2 +/- 1 to 11 +/- 3 hours. The half-life in women tended to be slightly longer

than in men, but the difference was not significant. Hepatic cirrhosis resulted in a marked decrease in the clearance of buspirone,
which correlated with serum alkaline phosphatase activity. Renal disease produced a modest and metyrapone.

Pharmacokinetic drug interactions

Erythromycin and itraconazole

Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. The greatly elevated plasma buspirone concentrations resulted in increased effects.

CYP3A-mediated drug-drug interaction

In the rat model, the mean plasma $AUC_{0\text{-}inf}$ of buspirone (10 mg/kg, p.o.) was increased by 7.4-fold and 12.8-fold after co-administration with ketoconazole and ritonavir (20 mg/kg, p.o.), respectively. The mean plasma $AUC_{0\text{-}inf}$ of verapamil (10 mg/kg, p.o.) was increased by 3.0- fold and 4.8-fold after co-administration with ketoconazole and ritonavir (20 mg/kg, p.o.), respectively. Thus, the rat DDI model correctly identified buspirone as a sensitive CYP3 substrate (>5-fold AUC change) in contrast to verapamil. In addition, for both victim drugs, the extent of DDI when co-administered was greater with ritonavir compared with ketoconazole, in line with their in vitro CYP3A inhibition potency in RLM.

Fluvoxamine

The anxiolytic action of co-administration of tandospirone (similar/ equivalent to buspirone) and fluvoxamine was examined using the rat contextual conditioned fear stress model. One day after fear conditioning, both tandospirone (60 mg/kg, p.o.) and fluvoxamine (60 mg/ kg, p.o.) significantly inhibited conditioned freezing and their combination effect was additive. In addition, plasma concentration of tandospirone was increased by fluvoxamine. Conclusions: There is a CYP3A4-related drug–drug interaction between tandospirone and fluvoxamine. Therefore, fluvoxamine may facilitate the anxiolytic effect of tandospirone via CYP3A4 inhibition.

III.4 Toxicology

The acute toxicity of buspirone has been established in various animal. The oral LD, is as follows for several animal species:

- rats 196 mg/kg;
- monkeys 356 mg/kg;
- dogs 586 mg/kg;
- mice 655 mg/kg.

These doses are 160-550 times the recommended daily dose for humans.

Repeated-dose toxicity

No gross or microscopic evidence of tissue damage was detected in rats and monkeys with buspirone administration of 50-200 mg/kg and 37.5-150 mg/kg, respectively, for 3 months. Toxic effects were noted at these mid- to high-dose levels. In rats, slight reductions in weight gain, and altered glucose and protein values were measured. In monkeys, CNS toxicities were manifested by ataxia, tremors, catatonia, and hypoactivity.

Oral administration of buspirone to rats 48-160 mg/kg/day and to monkeys 25-1 00 mg/kg/ day over 12 months resulted in similar CNS manifestations.

Buspirone was added to the diet of rats (24 months) and mice (78 weeks) to detect any possible long-term adverse effects. Dosages were 48-160 mg/kg/day in rats and 50-200

mg/kg/day in mice. No microscopic evidence of neoplasms or tissue masses was detected in various organs. The only drug-related histopathologic
finding in rats treated for 2-4 months was nonprogressive pulmonary histiocytosis. The pulmonary change in rats were similar at weeks 52 and 104. Pulmonary histiocytosis was not seen in mice or monkeys treated over the long term.

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finding in rats treated for 2-4 months was nonprogressive pulmonary histiocytosis. The pulmonary change in rats were similar at weeks 52 and 104. Pulmonary histiocytosis was not seen in mice or monkeys treated over the long term.

When buspirone is given by a parenteral route (IP, IV) lethal doses are lower in the same species. Toxic CNS signs are clonic convulsions, ataxia and tremors. The toxic effects of oral buspirone on rats and monkeys were studied for three consecutive months. Doses up to 50 mg/kg/day produced no remarkable toxic effects in either species. Toxic effects such as reduced weight gain and a slight decrease in red blood cells, hematocrit and haemoglobin concentration were seen in rats at 50-200 mg/kg/day.

In monkeys, administration of 75-150 mg/kg/day produced hypoactivity, ataxia, tremors, catatonia and hematologic changes similar to those in rats. Oral administration of buspirone to rats and monkeys at 80-160 mg/kg/day and 50-100 mg/kg/day for 12 consecutive months produced various CNS effects (sedation and anorexia), increases in liver, kidney, heart and adrenal weights, and a decrease in testicular weight, especially at higher doses. No gross or microscopic changes were observed with the exception of histiocytosis in rats and decreased resistance to gastrointestinal infection in monkeys.

In a reproduction study, rats were treated with buspirone where no-effect dose level of oral buspirone under the present experimental condition was estimated to be 2 mg/kg/day against dams and their offspring.

Buspirone was not a mutagen in the following tests: Salmonella typhimurium (Ames test); mouse lymphoma cell cultures; in vitro DNA synthesis (WI-38 human cell line); and in vivo chromosomal aberrations using mouse bone marrow.

A study evaluated nefazodone, another triazolopyridine trazodone, plus the azaspirodecanedione buspirone, for cytotoxicity and effects on mitochondrial function. Of the three antidepressants evaluated, the data indicated that nefazodone is cytotoxic to HepG2 cells grown in either glucose or galactose, although the latter are significantly more susceptible. This was also the case for trazodone, and to a lesser extent buspirone which had only modest toxicity to glucose-grown cells. This potency rank order was corroborated via metabolic profiling and via monitoring respiration of isolated rat liver mitochondria.

Genotoxicity
Genotoxic and carcinogenic effects of antipsychotics were reviewed in assays conducted on rodent models. Buspirone gave negative responses in all genotoxicity assays and were not carcinogenic in rodents.

Reproductive and developmental toxicity
Reproduction studies in rats treated with buspirone 9, 18, or 36 mg/kg/day showed no impairment of fertility. No skeletal or visceral abnormalities or other findings indicated that a teratogenic or embryotoxic effect in rats or rabbits occurred during embryogenesis. Pregnant rats were treated with buspirone during the last third of pregnancy and 3 weeks postnatally. No evidence of adverse effects on fetal development, birth weight, growth, or survival was noted. Buspirone and metabolites are excreted in the breast milk of rats. Buspirone was not a mutagen in the following tests: Salmonella typhimurium (Ames test); mouse lymphoma cell cultures; in vitro DNA synthesis (WI-38 human cell line); and in vivo chromosomal aberrations using mouse bone marrow.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for a products containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

A justification to support the establishment of a pharmaceutical bridge between applicant's product and the product(s) described in the literature was provided. Data has been submitted to justify that a BCS biowaiver is acceptable based on evidence that buspirone hydrochloride is highly soluble with complete absorption, high permeability (BCS class I) and is not considered to be a narrow-therapeutic drug and the products are immediate release solid dose preparations for oral use with the same pharmaceutical form as the products described in the literature and excipients present in proposed applicant's product have no potential to affect absorption.

The Applicant has also provided comparative *in vitro* dissolution data against the licensed generic product Buspirone 5mg and 10 mg Tablets (PL 00142/0455 and PL 00142/0455).
The literature references provide adequate evidence of a pharmaceutical bridge between the Applicant's product and the product described in the literature; providing suitable assurance that dissolution performance of buspirone tablets is typically rapid and completed (>85% in 15 min).

IV. 2 Pharmacokinetics

Absorption Distribution
When administered orally, the drug is rapidly and completely absorbed and undergoes extensive firstpass metabolism, having a mean bioavailability in humans of approximately 4%

The pharmacokinetics of 14C-labeled buspirone was studied in eight healthy males after 20 mg oral and 1 mg intravenous administration. Buspirone was rapidly absorbed after oral administration, with a peak serum concentration time (Tm,) at 0.78 hours ± 0.21.
The objective of a study was to evaluate the absorption of buspirone and its biotransformation to 1-(2-pyrimidinyl) piperazine (1-PP) from two different extended-release (ER) formulations of buspirone HCl tablets (12-hour and 24-hour in vitro release) and from a commercially available immediate- release (IR) tablet. A single dose of the 30 mg ER tablets was compared with two doses of the 15 mg IR tablet administered 12 hours apart. Eighteen healthy male subjects participated in this randomized, open-label, three-treatment crossover study. Blood samples were obtained at 22 time points from pre-dose (0 hour) until 36 hours post-dose, and plasma concentration of buspirone and 1-PP was determined by
LC/tandem mass spectrometry method. The pharmacokinetic parameters AUC0-t, AUC0-∞, Cmax, tmax, Kel, and t1/2 were calculated and statistically analyzed. The results indicated extended release of buspirone from the two test products in vivo with a 70% to 90% greater bioavailability in comparison with the IR formulation. The bioavailability of 1-PP from ER formulations appears to be equal to that from the IR formulation. Both buspirone ER tablets successfully delivered bioavailable buspirone with a reduction in peak drug and metabolite plasma levels, prolonged buspirone plasma concentrations, and decreased ratio of 1-PP to buspirone concentration with less intersubject variation when evaluated as a single-dose study in healthy human subjects.
A 21-day, open-label, multisite, dose escalation study comprising three demographic groups (children, adolescents, and adults) was performed to determine the pharmacokinetics and tolerability of orally administered buspirone. Thirteen children and 12 adolescents with anxiety disorder and 14 normal healthy adults were escalated from 5 to 30 mg buspirone bid over the 3-week study. Pharmacokinetic analysis revealed that buspirone was rapidly absorbed in all study groups, reaching peak levels at about 1 hour after administration. Peak plasma buspirone concentrations (Cmax) were highest in children and lowest in adults at all three dose levels (7.5, 15, 30 mg bid). However, 1-PP, the primary metabolite of buspirone, exhibited a different plasma concentration-time profile; Cmax was significantly higher in children than in either adolescents or adults at all concentrations. In addition, TAUC0-T for 1-PP was significantly higher in the children cohort relative to adolescents and adults. Buspirone was generally safe and well tolerated at doses up to 30 mg bid in adolescents and adults and most of the children. The most frequently reported adverse events in children and adolescents were light headedness (68%), headache (48%), and dyspepsia (20%); 2 children withdrew from the study at the higher doses (15 mg and 30 mg bid) due to adverse effects. In adults, the most common adverse effect was somnolence (21.4%); light headedness, nausea, vomiting, and diarrhea were also reported, although these were mild in intensity.

The objective of this study was to assess the pharmacokinetics of 6-hydroxybuspirone (6OHB) when given orally via three forms: racemate (BMS-528215), S-enantiomer (BMS-442606) and R-enantiomer (BMS-442608), versus following the administration of buspirone. A double-blind, randomized, fourperiod, four-treatment, crossover study balanced for residual effects in healthy subjects was conducted (n ¼ 20). Subjects received single 10 mg doses of each compound in a randomized fashion with pharmacokinetics determined over a 24 h period. There was a 4-day washout between each dosing period. All three forms of 6OHB (racemate, S-enantiomer and R-enantiomer) were well tolerated. There was interconversion between enantiomers. The dominant enantiomer was the S-enantiomer no matter which form of 6OHB was administered. All three forms of 6OHB produced approximately 2- to 3-fold greater exposure to total 6OHB than did buspirone. All three forms produced equal exposure to 1-(2-pyrimidinyl)-piperazine (1-PP) which was approximately 30% less than the 1-PP exposure derived from buspirone administration. All three forms of 6OHB produced approximately 3-fold higher 6OHB:1-PP ratios and approximately 2.5- fold higher total 6OHB exposures than did buspirone administration. All compounds were well tolerated. There seemed to be no advantage of one of the enantiomers of 6OHB over the racemate.
The volume of distribution of the central compartment of buspirone is 5.3 L/kg. Plasma protein binding of buspirone is >95% and buspirone is bound to both albumin and α1-acid glycoprotein. Buspirone is highly protein bound (more than 95 percent), interacting with both albumin and alpha-acid glycoprotein. However, buspirone did not displace dilantin, propranolol, digoxin, or warfarin from plasma proteins.

Effect of Food
The effect of food on the pharmacokinetics of buspirone was evaluated in 8 healthy individuals in a 2-way crossover design study following an oral dose of buspirone 20mg. Buspirone was administered 15 minutes after the meal following an overnight fast. The postprandial AUC was 80% higher than the preprandial value (14.8 ng.hr/ml ± 2.58 vs 8.03 ng.hr/ml±1.72). The results of the study indicated that food increased the area under the concentration- time curve (AUC) and the Cmax of buspirone almost 2-fold, whereas there was negligible change in tmax and half-life between fed and fasting states.

Metabolism and Elimination
Buspirone undergoes extensive pre-systemic and systemic metabolism including CYP3A4-dependent N-dealkylation to 1-aryl-piperazines. These metabolites are best known for the variety of serotonin receptor-related effects they cause in man and animals, although some have affinity for other neurotransmitter receptors; others. Once formed they distribute extensively in tissues, including brain which is the target site of most arylpiperazine derivatives, and are then primarily biotransformed by CYP2D6-dependent oxidation to hydroxylates which are excreted as conjugates; only 1-(2- benzisothiazolyl)-piperazine is more susceptible to sulfur oxidation than to aromatic hydroxylation. In studies analysing animal brain and human blood, 1-aryl-piperazine concentrations were either higher or lower than the parent compound(s), although information is available only for some derivatives. At steady state, the metabolite-to-parent drug ratios varied widely among individuals taking the same dosage of the same arylpiperazine derivative. This is consistent with the known individual variability in the expression and activity of CYP3A4 and CYP2D6.

Buspirone forms 1-PP during its biotransformation in rats and man. After oral administration in man given the anxiolytic dose (20 mg) of Buspirone, the metabolite reached higher plasma Cmax values than its parent drug. Its plasma elimination t1/2 was more than double that for Buspirone . These results, together with the fact that 1-PP is biochemically and pharmacologically active, suggested that the metabolite may contribute significantly to the central effects of the parent drug.
The metabolism and disposition of buspirone was studied in the rat, the monkey, and in more than 150 human subjects. Buspirone is eliminated primarily by oxidative metabolism, which produces several hydroxylated metabolites, including 5-hydroxy-buspirone and 1-pyrimidinylpiperazine. The latter metabolite is from 1 to 20 percent as potent as buspirone in a variety of pharmacologic tests; 5- hydroxybuspirone is essentially inactive.
The objective of a study was to assess the pharmacokinetics of an active metabolite of buspirone, 6- hydroxybuspirone (6OHB), over the therapeutic dose range of buspirone. A 26-day, open-label, nonrandomized, single-sequence, dose-escalation study in normal healthy volunteers was conducted (N= 13). Subjects received escalating doses of buspirone with each dose administered for 5 days starting at a dose of 5 mg twice daily and increasing up to 30 mg twice daily. Plasma concentrations of 6OHB were approximately 40-fold greater than those of buspirone. 6OHB was rapidly formed following buspirone administration, and exposure increased proportionally with buspirone dose.
This study was carried out to determine the metabolic pathways of buspirone and cytochrome P450 (P450) isoform(s) responsible for buspirone metabolism in human liver microsomes (HLMs). Buspirone mainly underwent N-dealkylation to 1-PP, N-oxidation on the piperazine ring to buspirone N-oxide (Bu N-oxide), and hydroxylation to 3'-hydroxybuspirone (3'-OH-Bu), 5-hydroxybuspirone (5-OH-Bu), and 6'-hydroxybuspirone (6'-OH-Bu) in HLMs. The apparent K(m) values for buspirone metabolite formation in pooled HLMs were 8.7 (1-PP), 34.0 (Bu N-oxide), 4.3 (3'-OH-Bu), 11.4/514 (5-OH-Bu), and 8.8 microM (6'-OH-Bu). CYP3A inhibitor ketoconazole (1 microM)
completely inhibited the formation of all major metabolites in HLMs (0-16% of control), whereas the chemical inhibitor selective to other P450 isoforms had little or no inhibitory effect. Recombinant CYP3A4, CYP3A5, and CYP2D6 exhibited buspirone oxidation activities among nine P450 isoforms tested. The overall metabolism rate of 5 microM buspirone by CYP3A4 was 18-fold greater than that by CYP2D6 and 35-fold greater than that by CYP3A5. In a panel of HLMs from 16 donors, buspirone metabolism correlated well CYP3A activity ($r2 = 0.85-0.96$, $rho < 0.0005$), but not the activities of other P450 isoforms. The metabolism rates of buspirone in CYP2D6 poor-metabolizer genotype HLMs were comparable to those in pooled HLMs. Taken together, these data suggested that CYP3A, mostly likely CYP3A4, is primarily responsible for the metabolism of buspirone in HLMs

The metabolism of an oral dose (20 mg) of the antianxiety drug buspirone labeled with 14C/15N was studied in human subjects. 15N was incorporated in the molecule to facilitate structural characterizationof the metabolites by mass spectrometry. Urine samples were collected at intervals up to 24 hr and analyzed for radioactivity. Cumulative urinary excretion accounted for 50% of the dose in 24 hr. The urine was hydrolyzed with beta glucuronidase/arylsulfatase and the deconjugated metabolites were isolated and purified by HPLC. The purified metabolites were identified by GC/MS, 1H-NMR, and

comparison with authentic standards when available. Seven metabolites of buspirone were identified unambiguously, together with unchanged drug. Hydroxylation alpha to the glutarimidyl carbonyl at the 6'-position on the spiro ring system, hydroxylation at the 5-position on the pyrimidine ring, and Ndealkylation of the butyl-substituted side chain were major routes of metabolism. The identifiedmetabolites accounted for 88% of the total radioactivity in the urine.

Pharmacokinetics in special populations

Elderly population

Twenty-four men and 24 women ages 20-77 years received a single 15 mg oral dose of buspirone followed by 4 days of 15 mg tid administration. Plasma concentrations of buspirone and 1-PP following both single and multiple dosing were determined by RIA and GCMS, respectively.

There were no significant differences between the young and elderly of either gender with regard to buspirone AUC, Cmax, Tmax and half-life values. The 1-PP AUC values were higher for young of either gender compared to the corresponding group of elderly subjects and the 1-PP Cmax values were higher for women than men. These differences are unlikely to be of clinical significance.

The buspirone and 1-PP AUC values for a dosing interval during multiple dosing are not significantly different than the respective single dose AUC values. Buspirone treatment was well-tolerated by all subjects even though the 45 mg/day dose was 3 times the recommended starting dose in clinical practice.

Overall, the lack of marked or consistent differences in buspirone or 1-PP pharmacokinetics in elderly subjects compared to younger subjects of the same gender suggested there is no need to alter the initial dose of buspirone based solely on patient age.

Renal/Hepatic impairment

The single dose and steady-state pharmacokinetics of buspirone and its metabolite 1-PP was evaluated in normal volunteers and patients with renal or hepatic impairment, using a parallel group design, with assignment of patients to study group on the basis of the degree of renal (mild, moderate, severe) or hepatic (compensated or decompensated) impairment. Each healthy volunteer or patient received a single dose of 10 mg buspirone on Day 1 of the study, and starting 36 h after the first dose, healthy volunteers and patients received 10 mg doses of buspirone every 12 hours for 9 days. On the morning of Day 10 they received the last dose. Serial blood samples were collected on Days 1, 5 and 10 and plasma was analysed for buspirone and 1-PP. The plasma concentrations of buspirone and 1-PP were highly variable regardless of the renal or hepatic function. The peak concentrations (Cmax) and area under the curves (AUC) of buspirone and 1-PP on Days D5 and 10 were higher than on Day D1. The trough levels (Cmin) and AUCs (D5 and 10) of buspirone and 1-PP indicated, that, regardless of renal or hepatic function, steady state was reached after 3 to 5 days of dosing. At steady-state, patients with renal or hepatic impairment had significantly higher Cmax and AUC values of buspirone than in normal volunteers. However, the intensity and frequency of adverse experiences in patients with renal or hepatic impairment were not significantly different from those observed in normal volunteers.

Twelve patients with mild to moderate impairment of renal function and 12 healthy subjects each received 20mg buspirone as a single dose in this acute study. Six anuric patients with chronic renal failure were given two 20mg doses of buspirone, the first 2 days before haemodialysis (between dialyses) and the second during hemodialysis (2 hours before dialysis began). The differences betweenthe median pharmacokinetic values of buspirone for healthy subjects, patients with mild to moderate renal impairment, and anuric patients were not statistically significant. Similarly, there were no significant differences between values in mild to moderate renal failure vs healthy subjects. Some of the median pharmacokinetic values for the active buspirone metabolite 1-PP, however, differed significantly for anuric patients, compared with healthy subjects or patients with mild to moderate renal impairment. When assessed between and during haemodialysis, the anuric patients had significantly (p less than 0.05) greater pharmacokinetic median values: half-life (t 1/2) = 15.2 vs 9.8 hours; area under the concentration-time curve (AUC) = 604 vs 404 nmol/L.h; and mean residence time (MRT) = 9.28 vs 6.96 hours. No firm recommendation for specific dosage can be made based on the present data.
However, it does appear that in patients with mild to moderate renal impairment, the pharmacokinetics of buspirone and its active metabolite 1-PP are similar to those in individuals with normal renal function. For anuric patients higher concentrations of the 1-PP metabolite are attained while they are not undergoing haemodialysis. A dosage reduction of 25 to 50% might be necessary when buspirone is given to anuric patients.

IV.3 Pharmacodynamics

Mechanism of action

Biochemical and electrophysiologic studies indicate that buspirone alters monoaminergic and GABAergic systems in a manner different from that of the benzodiazepines. The uniform depressantaction of the benzodiazepines upon serotonergic, noradrenergic, and dopaminergic cell firing may result from their facilitatory effect on gamma-aminobutyric acid and its known inhibitory influence in these monoaminergic areas. Unlike the benzodiazepines, buspirone exerts a differential influence upon monoaminergic neuronal activity, suppressing serotonergic activity while enhancing dopaminergic and noradrenergic cell firing. The mechanism of action of buspirone challenges the notion that only one neurotransmitter mediates anxiety. The interaction with multiple neurotransmitters at multiple brain sites suggests that buspirone may alter diverse activities within a "neural matrix of anxiety." In contrast to the benzodiazepines, buspirone orchestrates activity within this neural matrix to achieve effective treatment of anxiety while preserving arousal and attentional processes. Alterations of serotonergic neurotransmission are involved in the underlying pathology of a variety of psychiatric disorders, including anxiety and depression. Although the exact mechanism of action of buspirone is unknown, the anxiolytic properties of the drug are believed to result primarily from its effects on central serotonergic systems. Binding to serotonin 5-HTIA receptors in the brain is the primary pharmacological action of buspirone. 5-HTIA receptors are found both presynaptically and postsynaptically and the activity of buspirone appears to differ at these distinct sites. Presynaptically, buspirone acts as a full agonist at 5-HTIA receptors located in the dorsal raphe nucleus. Binding to these receptors inhibits the activity of serotonergic neurons through downregulation. At postsynaptic hippocampal5-HTIA sites, buspirone acts as a partial agonist (i.e. buspirone has less activity than an endogenous full agonist such as serotonin.
In addition to its effects on serotonin neurotransmission, buspirone also has a moderate affinity for presynaptic dopamine D2 receptors. However, whether this affinity contributes to the anxiolytic properties of buspirone is not known. Unlike benzodiazepines, buspirone does not bind to the yaminobutyric acid (GABA) benzodiazepine complex or inhibit benzodiazepine binding in vitro; it has no effect on the binding of benzodiazepines and nor is

the action of buspirone blocked by the benzodiazepine receptor antagonist flumazenil.
Figure 2: GABA-benzodiazepine receptor chloride ionophore complex.
GABA-benzodiazepine receptor chloride ionophore complex: the interaction of pharmacologic agents with this supramolecular complex has been proposed to result in a number of therapeutic actions, including anxiolysis. It has been hypothesized that compounds which bind to benzodiazepine receptors may produce a spectrum of pharmacologic actions ranging from anxiolysis to anxiety and convulsions. In a double-blind study, 56 adult psychoneurotic outpatients with a primary diagnosis of anxiety neurosis were randomly assigned to receive buspirone (N = 18), diazepam (N = 20), or placebo (N = 18) over a four-week period. A battery of tests administered weekly indicated that buspirone was as effective an antianxiety agent as diazepam and produced no more and perhaps fewer side effects. Buspirone showed excellent antidepressant effects as well. If further studies confirmed the authors' findings and determine that buspirone does not result in tolerance and addiction, it would be more advantageous than the benzodiazepines in the treatment of anxiety.

Pharmacodynamics Studies

[carbonyl-11C]WAY-100635 is a radioligand which can be used with positron emission tomography (PET) to provide high contrast delineation of human brain regions that are rich in 5-HT1A receptors. In a PET study, the binding of [carbonyl-11C]WAY-100635 was characterized in the cynomolgus monkey brain. Pre-treatment with each of the two reference compounds, WAY-100635 and 8-OHDPAT, as well as the drugs buspirone and pindolol, induced a marked inhibition of [carbonyl11C]WAY-100635 binding in the neocortex and the raphe nuclei. A preliminary Scatchard analysis yielded 5-HT1A receptor density values of the same order as those that have been reported *in vitro*. The study showed that [carbonyl-11C]WAY-100635 binds specially to 5-HT1A receptors in the primate brain and has potential for determination of 5-HT1A receptor occupancy and density in psychiatric patients.

The 5-HTlA receptor appears to be negatively coupled to the adenylate cyclase system and opens potassium channels via the G protein Gi, closes calcium channels via Go and may also stimulate phosphoinositide turnover, (Emerit et al, 1987) Thus, 5-HTIA receptors are linked with multiple G protein [guanosine triphosphate (GTP) building protein] effective systems. It has been suggested that pre- and postsynaptic 5-HTlA receptors are distinct and further suggest that 5-HTIA agonists act as partial agonists postsynaptically but as full agonists presynaptically in the dorsal raphe. Raphe nuclei serotonin neurons appear to be regulated by presynaptic 5-HTIA autoreceptors. The azapirones completely inhibit neuronal firing in vivo when applied to dorsal raphe nucleus neurons, thus showing that these agents are full agonists at presynaptic 5-HTlA autoreceptors.

Acute activation of presynaptic 5-HTIA receptors results in a decrease in neuronal firing of serotonergic neurons and a reduction in serotonin release. The azapirones also act as partial agonists at postsynaptic hippocampal 5-HTIA sites. A partial agonist binds to a receptor but exerts less effect than does an endogenous full agonist (e.g. serotonin).

Having partial agonist effects confers unique properties on molecules. When partial agonists are in an environment relatively devoid of full agonists (e.g. serotonin), their intrinsic agonist properties areexpressed. However, when both partial agonists and full agonists are in the same environment (in the test tube or synapse), they compete for receptor binding sites. Because partial agonists bind to receptors but contribute less to synaptic activation than do full agonists, the resulting agonist activity is less than would have been achieved by the full agonist alone. Thus, by displacing full agonists with greater intrinsic activity from receptor sites, partial agonists appear to function as antagonists.

Buspirone metabolite (1-PP) does not bind to 5-HTlA receptors but acts *in vivo* and *in vitro* as an α2-arenoreceptors antagonist. The anxiolytic effects of 1-PP are weak and present only

at high doses. Buspirone unlike gepirone, has a high affinity for dopamine receptors.

Pharmacodynamic drug interactions
MAO inhibitors (including anti-depressants)
Use of monoamine oxidase inhibitors (MAOI) within 14 days before or after buspirone therapy due to risk of serotonin syndrome and/or elevated blood pressure (Wilson et al, 2019) Phenelzine should also not be used in combination with buspirone hydrochloride, since several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone hydrochloride. At least 14 days should elapse between the discontinuation of Phenelzine and the institution of another antidepressant or buspirone hydrochloride, or the discontinuation. Baclofen, lofexidine, nabilone, antihistamines may enhance any sedative effect.

IV.4 Clinical efficacy

Comparative studies
The aim of a study was to evaluate the efficacy and safety of sertraline and buspirone in the treatment of elderly patients with GAD. Based on selection criteria, 46 patients were recruited who met DSM-IV criteria for GAD. Patients were randomly assigned to sertraline (50-100 mg/day) or buspirone (10-15 mg/day) for 8 weeks in a single-blind trial. The primary outcome measure used in the present study was the Hamilton Rating Scale for Anxiety (HRSA). Both sertraline and buspirone had significant anxiolytic efficacy. A steady decrease in the total HRSA scores for both groups was observed throughout the study period. After 2 and 4 weeks, buspirone was found to be significantly superior to sertraline ($P < 0.001$), but at the end of study period this difference did not reach statistical significance ($P = 0.16$). The mean HRSA score after 8 weeks significantly decreased in subjects treated with sertraline ($P < 0.001$), and buspirone ($P < 0.001$). No clinically adverse events or changes in laboratory test results were observed during the study period. Both sertraline and buspirone appear to be efficacious and well tolerated in the treatment of GAD in elderly patients.
Psychomotor and psychologic effects of single doses of buspirone (10 and 20 mg) and lorazepam (2.5 mg) alone or combined with alcohol (I gm/kg) were investigated in 12 healthy young men. Crossover study in 12 healthy young men. Lorazepam alone impaired psychomotor skills (tracking, body balance, extraocular muscle balance, and flicker recognition), the effects being maximal at 180 min. This impairment was not subjectively perceived by the subjects. Neither dose of buspirone alone impaired objective measurements, although buspirone, especially in the 20-mg dose, was felt to cause drowsiness, weakness, and faintness.
In a study, 33 outpatients with generalized anxiety disorder were entered into a crossover study of 3 weeks each of placebo, buspirone 10 to 30 mg daily, and diazepam 10 to 30 mg daily. Psychiatrist and patient ratings were made, together with psychological tests and EEG and skin conductance measures before and after each treatment. Of the nine dropouts, six were on buspirone at the time of dropout. For the remaining 24 patients, the mean daily doses attained of buspirone and diazepam were both 20 mg.

On most clinical ratings diazepam was superior to buspirone and placebo, which did not differ. Diazepam produced minor psychomotor changes and the expected major effects on the EEG. Buspirone was without effect. Side effects on buspirone were mainly nausea and giddiness and on diazepam, drowsiness.

A study was aimed to compare the efficacy and safety of augmenting paroxetine with risperidone, buspirone, valproate, trazodone, or thyroid hormone in patients with treatment-resistant depression (TRD), 225 patients with retrospectively and/or prospectively identified stage II TRD were randomly assigned to receive an 8-week treatment of paroxetine 20 mg/d augmented with risperidone 2 mg/d (n = 45), sodium valproate 600 mg/d (n = 39), buspirone 30 mg/d (n = 46), trazodone 100 mg/d (n = 47), or thyroid hormone 80 mg/d (n = 48). The primary outcome was the remission rate defined as the 17- item Hamilton Rating Scale for Depression score of 7 or less at the end of study. Secondary outcomes included remission rate based on the Self-rating Depression Scale score of 50 or less at the end of study, response rate based on 17-item Hamilton Rating Scale for Depression total score of 50% improvement or greater from baseline, and the change in scores of Clinical Global Impression-Improvement scale, the Short Form 36 Health Survey, and the Life Satisfaction Rating Scale. The remission rates were 26.7% for risperidone, 48.7% for valproate, 32.6% for buspirone, 42.6% for trazodone, and 37.5% for thyroid hormone. There was no statistical significance among treatment arms in remission rates, secondary outcome measures, and adverse events. Risperidone, valproate, buspirone, trazodone, or thyroid hormone augmentation to paroxetine 20 mg/d was effective and well tolerated in Chinese patients with TRD.

A total of 66 outpatients meeting Diagnostic and Statistical Manual (DSM-III) criteria for generalized anxiety disorder began treatment in a randomized double-blind study that compared the efficacy and safety of buspirone and diazepam. Thirty-nine outpatients completed the 4-week trial. Both drugs were administered in a 1:1 dosage ratio; the daily prescribed dose did not exceed 40 mg. The mean daily dose of buspirone prescribed throughout the study was significantly higher than that of diazepam. Diazepam had a significantly earlier onset of efficacy than buspirone, although both drugs were equivalent after 4 weeks of treatment. Adverse reactions were more frequent in the diazepam group. Total scores from the Hamilton anxiety scale and physician's global ratings show that diazepam was significantly superior to buspirone during the initial 2 weeks of treatment. These findings are further corroborated by the results of patients' self-rated scales.

In a controlled, randomized, multicenter, double-blind study involving 335 patients with generalized anxiety disorder, buspirone was compared to lorazepam, diazepam or bromazepam in order to test its global efficacy, preferential effectiveness in defined subgroups of patients or symptoms, latency of action and safety and tolerability. Apart from minor differences, the dropout rate, the number of subjects for whom the dose was increased, the number of capsules taken daily, the modifications of HRSA, VAS 100 mm, CGIS and CGSRS, the curves of improvement over time, the effectiveness on the somatic and psychic factors of the HRSA, the responsiveness of depressed and non-depressed anxious patients, and the profiles of adverse events indicated clinical equivalence between the azaspirodecanedione and the comparison benzodiazepines.

Fifty-one out-patients presenting with generalised anxiety disorder were included in a double-blind trial and treated with either buspirone or diazepam over 6 or 12 weeks, after which they were abruptly withdrawn and continued on placebo to 14 weeks. Ratings of anxiety and other symptoms were administered fortnightly and additional withdrawal symptoms noted. Forty patients completed the study; 8 of the 11 drop-outs were taking buspirone. Both drugs reduced anxiety, diazepam more rapidly, but with greater withdrawal symptoms, particularly after 6 weeks. Regular treatment with diazepam for 6 weeks leads to a significant risk of pharmacological dependence that is not present with buspirone. The anxiolytic activity, the tolerance, and the withdrawal symptoms of buspirone and oxazepam were compared in two groups of 14 and 12 outpatients, respectively, suffering from generalized anxiety in a double-blind study with random allocation of patients. The 6-week active period was preceded and followed by 1 and 2 weeks on placebo, respectively. Clinical assessments were performed before and after the predrug placebo period and every 2 weeks thereafter and included Hamilton anxiety and depression scales and AMDP anxiety subscale. The initial daily dose was 15 mg buspirone or 45 mg oxazepam in 3 intakes and the mean final daily doses were 22.2 and 55.8 mg, respectively. Results showed a slower anxiolytic activity of buspirone compared to oxazepam with less improvement after 2 weeks of treatment. The rebound anxiety following abrupt discontinuation of the drug and the level of side effects did not significantly differ between the two compounds.
The efficacy and safety of alprazolam and buspirone for treating generalized anxiety disorder (GAD) were compared in a 6-week, double-blind, randomized, placebo-controlled study of 94 outpatients. Mean daily doses at the end of the study were 1.9 mg alprazolam and 18.7 mg buspirone. As judged by the Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale, Physician's Global Improvement Scale, and other efficacy scales, alprazolam and buspirone were similar in efficacy, but more effective than placebo, for treating anxiety and depression symptoms in these patients. Clinically important differences were noted between drugs in the onset of effect, with alprazolam producing rapid and sustained improvement within the first week of treatment and buspirone producing more gradual, continuous improvement throughout the study. Significantly more buspirone-treated than alprazolam treated patients failed to complete the study, primarily because of side effects or inefficacy. No clinically important differences were noted between alprazolam and buspirone in side effects, vital signs, or laboratory test results. Alprazolam-treated patients most frequently reported central nervous system related side effects (drowsiness and sedation), while buspirone-treated patients most frequently reported gastrointestinal system-related side effects (appetite disturbances and abdominal complaints).

Review study/Meta-analysis
The azapirone class of anxiolytic drugs is being evaluated for clinical use in the treatment of depression. Buspirone, a serotonin (5-hydroxytryptamine, 5-HT) partial agonist active at the 5-HT1A receptor subtype, was evaluated in the treatment of depression in a series of five placebo-controlled, parallel group studies involving 382 patients with DSM-III major depression and significant associated anxiety symptoms (both Hamilton depression [HAM-D] and Hamilton anxiety [HAM-A] scales greater than or equal to 18). Buspirone therapy was initiated at 15 mg/day with individual dose titration to a maximum of 90 mg/day and resulted in marked improvement in both depressive and anxiety symptoms. Analyses of the composite data base from the five studies show significant (p less than 0.05)

improvement in mean HAM-D, HAM-A, and Clinical Global Impression-Global Improvement scale ratings for buspirone-treated compared with placebo-treated patients. Of particular interest was significant improvement in cardinal depression symptoms, e.g., depressed mood, guilt, work and interest, anergia, and diurnal variation of mood. Subset analyses revealed that patients with melancholic-type major depression and patients with more severe symptoms (judged by higher initial HAM-D or HAM-A total scores) responded better to buspirone than did patients who were less ill. The buspirone dose most frequently associated with clinically significant improvement was 40 mg/day.

Dose and administration

Buspirone therapy was associated with greater retention in the 12-week treatment trial, reduced anxiety, a slower return to heavy alcohol consumption, and fewer drinking days during the follow-up period.

Buspirone appears to have a useful role in the treatment of anxious alcoholics. Further research is needed to clarify which patient characteristics and concomitant treatments result in optimal response to buspirone therapy. Subjects initially received one single-dose capsule (ie, buspirone hydrochloride, 5 mg, or placebo) three times daily (TID). If tolerated, the doses were then increased every 3 to 4 days by one additional capsule TID to a maximum dosage of buspirone hydrochloride, 20 mg TID, or an equivalent number of placebo capsules. The maximal dose was generally reached by the end of the second week of treatment. The mean maximal daily dose was 10.5 (±2.7) tablets (52.5 [±13.5] mg) for buspirone hydrochloride treated subjects and 10.2 (±3.3) tablets for placebo treated subjects. This difference was not statistically significant (F[1,58]=0.12; P=.72). At the end of the 12-week treatment period, the medication therapy was tapered over a 3-day period and then discontinued.

A randomized, double-masked, comparative study evaluated the efficacy and safety of buspirone 30 mg/d, administered twice a day (BID) or three times a day (TID), in patients with generalized anxiety disorder (GAD), commonly called persistent anxiety. Patients who participated had GAD according to criteria of the Diagnostic and Statistical Manual of Mental Disorders. Third Edition, Revised, modified to include patients for whom the symptom duration was at least 4 weeks and scored ≥ 18 on the Hamilton Rating Scale for Anxiety (HAM-A). After a 7-day placebo lead-in phase, patients who continued to qualify were randomized to receive buspirone, titrated from 15 mg/d (5 mg TID) to 30 mg/d, as either a BID or TID regimen, for 8 weeks. Of the 137 patients who began the study, 120 patients were included in the data evaluation. Both buspirone BID and TID treatment groups demonstrated significant reductions in mean HAM-A total scores and improvement on Clinical Global Impression measures, with no significant differences detected between the two treatment groups for either measure at any time point. The overall incidence of adverse events was similar for both treatment groups, except for a significantly greater incidence of amblyopia in patients receiving buspirone 15 mg BID. In summary, there was no appreciable difference in efficacy or safety between buspirone 15 mg BID or 10 mg TID in patients with persistent anxiety.

In a meta-analysis report, safety results from two studies comparing buspirone 15 mg twice daily (BID) with buspirone 10 mg three times daily (TID) in patients with persistent anxiety are presented. In the study protocols, qualified patients completed a 7-day placebo lead-in phase and were randomized to receive buspirone 30 mg per day, as either a BID or TID regimen, for 6-8 weeks. A total of 289 patients received buspirone 15 mg BID (n = 144) or 10 mg TID (n = 145) at 15 sites. The incidence of adverse events was similar between the two treatment groups, except for a significantly greater incidence of palpitations in patients receiving buspirone BID (5%) compared to buspirone TID (1%). The most

frequently reported adverse events for both buspirone BID- and TID-treated patients were dizziness, headache, and nausea. No appreciable differences between treatments were observed for vital signs, physical exam, ECG, or clinical laboratory results. A change to BID dosing for buspirone may offer convenience and possibly higher compliance in patients with persistent anxiety without compromising the excellent safety and tolerability profile of the medication.
The maximum daily dosage of buspirone is 60 mg per day. In randomized controlled clinical trials, a typical range of therapeutic effect was between 15 to 60 mg per day of divided doses. The multiple dosing of buspirone, ranging from 5 mg twice daily to 30 mg twice daily, was safe and generally well tolerated. Buspirone at four doses of 5 to 30 mg bid was found to be safe and tolerable in patients diagnosed with an anxiety disorder and in healthy normal adults. There were no serious adverse events reported during these studies.

IV.5 Clinical safety

Buspirone is an azaspirodecanedione anxiolytic agent. Its mechanism of action is extremely complex, but investigations indicated that its main neuropharmacologic effects are mediated by the 5-HT1A receptors. Other neuroreceptor systems could be involved, as buspirone displays some affinity for DA2 autoreceptors and 5-HT2 receptors. It has been proposed that inhibition of synthesis and release of serotonin result through the combined interactions of neuroreceptors and secondary messenger systems. This action leads to inhibition of the firing rate of 5-HT-containing neurons in the dorsal raphe. From this profile, that differs from that of the benzodiazepines, buspirone lacks anticonvulsant and muscle-relaxant properties, and causes only minimal sedation.
Buspirone was well absorbed but is subject to first-pass metabolism. The mean systemic availability is approximately 4 percent. Buspirone is eliminated primarily by oxidative metabolism, which produces several hydroxylated metabolites, including 5-hydroxy-buspirone and 1-pyrimidinylpiperazine. In humans, the systemic exposure to buspirone increases linearly in relation to the oral dose. Food increases the bioavailability of buspirone by decreasing first-pass metabolism; absorption is not markedly altered. The pharmacokinetics of buspirone were not significantly different in men and women or in individuals 21 to 40 years old compared with those over 65 years of age. Half-life values observed in healthy volunteers ranged from two to 33 hours. Mean half-life values observed in healthy volunteers in the 14 studies conducted to date ranged from 2 ± 1 to 11 ± 3 hours. The half-life in women tended to be slightly longer than in men, but the difference was not significant. Hepatic cirrhosis resulted in a marked decrease in the clearance of buspirone, which correlated with serum alkaline phosphatase activity. Renal disease produced a modest decrease in buspirone clearance, which could not be correlated with an objective clinical measurement reflecting the severity of renal impairment.
Buspirone exhibits a very favourable safety profile. Abuse, dependence, and withdrawal symptoms have not been reported. The frequency of adverse effects is low, and the most common effects are headaches, dizziness, nervousness, somnolence and lightheadness. As a non-benzodiazepine, buspirone is a psychotherapeutic agent for the treatment of anxiety. It exhibits both a non-traditional clinical profile and a unique spectrum of activity within the central nervous system. In all types of clinical trials – placebo controlled, comparative, non-comparative and meta-analysis, buspirone was found to be effective in the treatment of anxiety from dose range 10 mg per day to 90 mg per day.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with buspirone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N