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Drug Evaluation

An assessment of iloperidone for the treatment of schizophrenia

Kewal K Jain

Jain PharmaBiotech, Bläsiring 7, CH-4057 Basel, Switzerland

Iloperidone (Novartis' Zomaril™) is an atypical antipsychotic agent for the treatment of schizophrenia. Current trends in the treatment of schizophrenia indicate that some atypical antipsychotics are being recommended as first-line therapy. Atypical antipsychotics, in addition to being dopamine (D) receptor antagonists, are all relatively potent serotonin (5-HT) receptor antagonists and are less likely than conventional dopamine antagonists to induce movement disorders. However, all of these agents differ in their receptor profiles and clinical profiles. Iloperidone, a benzisoxazole, is a mixed 5-HT_{2A}/D_2 antagonist. Iloperidone was found to be more potent than its analogues when compared with haloperidol in antagonising climbing behaviour in mice. Iloperidone is extensively metabolised and the main circulating metabolite is reduced iloperidone. In patients treated with iloperidone, a low incidence of extrapyramidal symptoms and weight gain has been shown. Data from Phase II trials demonstrated efficacy in patients at doses of 8 mg/day and tolerability was good up to 32 mg/day. Phase III prospective, double-blind, randomised trials with iloperidone are in progress under the ZEUS (Zomaril™Efficacy Utility and Safety) programme involving 3300 patients. Iloperidone, with a balance of activity at the dopaminergic and serotonergic receptors, has obvious advantages over clozapine and olanzapine, both of which have a similar receptor profile as they favour serotonergic over dopamine receptors. Iloperidone is likely to reach the market in 2001 and has favourable prospects in the atypical antipsychotic market for schizophrenia, which is expanding from US$ 1.5 billion in 2000 to US$ 3 billion in 2005.

Keywords: *atypical antipsychotics, dopamine receptors, extrapyramidal syndromes, iloperidone, psychosis, schizophrenia, serotonin receptors*

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1. Introduction

Iloperidone, an atypical antipsychotic agent, is in Phase III trials by Novartis for the potential treatment of schizophrenia. Atypical is the term used to describe antipsychotic drugs that produce minimal side effects, such as movement disorders, which were a typical feature associated with the use of classical antipsychotic agents. Clozapine (Novartis) was one of the first atypical antipsychotic agents and several more have been introduced since. Clozapine has a reduced tendency to produce any movement disorders, but is associated with agranulocytosis in rare cases, which requires blood count monitoring and restricts its use in some countries to patients who do not respond to conventional antipsychotics. This article will evaluate iloperidone for the treatment of schizophrenia. The disease and atypical antipsychotic agents will be described briefly as this topic has been covered in a previous article [1].

2. Overview of the disease

Schizophrenia is a severe and disabling psychiatric disorder that is characterised by delusions, hallucinations, disorganised speech or behaviour and flattened affect. Suicide is common in schizophrenic patients with 20% attempting suicide at some time and with up to 10% dying by suicide. Although the pathophysiology of schizophrenia has not been fully delineated, the pharmacological treatment has been dominated by the dopaminergic theory, which states that certain dopamine pathways are overactive in the disease. Cloning of genes for certain dopamine receptors has added a new dimension to research in this area. Evidence for the dopaminergic hypothesis is that antipsychotic drugs that block D_2 dopamine receptors are clinically effective. The main reason that clozapine appears to be an exception to the D_2 blockade hypothesis is that it has antipsychotic effects at dosages that do not cause the high levels of D_2 blockade (70%) seen with therapeutic dosages of other atypical and typical agents [2].

Serotonin has also been implicated in the pathogenesis of schizophrenia as post-mortem molecular studies show abnormalities in the 5-HT system. There are two changes in 5-HT receptor expression that seem to characterise the disease:

- An increase in 5-HT_{1A} receptor binding sites in frontal cortex, which is not accompanied by an increased 5-HT_{1A} receptor mRNA
- A loss of cortical 5-HT_{2A} receptors, which is paralleled by loss of its mRNA [3]

One way to resolve the conflicting information is to consider that both serotonin and dopamine receptors interact and play a part in the pathophysiology of schizophrenia.

Positron emission tomography (PET) has been used to study the role of brain receptors in schizophrenia [4]. Combination of PET with *in vivo* binding techniques provides information about the dopamine receptor distribution, number of binding sites and their affinity. Antipsychotic drugs have been shown to occupy dopamine D_2 receptors predominantly with some occupying D_1 receptors. PET studies using selective ligands have also visualised and quantified 5-HT receptors in the brains of schizophrenic patients [5].

2.1 Current management

Worldwide, most schizophrenic patients still receive conventional dopaminergic drugs, such as chlorpromazine and haloperidol, as first-line therapy and atypical antipsychotics are a second-line therapy. The trend is changing in Western countries and atypical antipsychotics (except clozapine) are being recommended as first-line therapy in Canada. The American Psychiatric Association practice guidelines of 1997 suggest either a high potency typical agent or an atypical agent other than clozapine as first-line treatment.

Atypical antipsychotics introduced during recent years (**Table 1**), in addition to being dopamine receptor antagonists, are all relatively potent 5-HT_{2A} antagonists and can be more appropriately described as 'serotonin-dopamine receptor antagonists'. However, all of these agents differ in their receptor profiles and therefore have different clinical profiles. Atypical antipsychotics are claimed to reduce positive (hallucinations and delusions) and negative (apathy, emotional withdrawal) symptoms of schizophrenia and are generally more effective than conventional antipsychotics against the negative symptoms. Atypical antipsychotic drugs have improved the quality of life for people with schizophrenia. The advantages of these over the conventional antipsychotics are that unlike conventional antipsychotics, they cause few movement disorders and they impair cognitive function to a much lesser degree than conventional antipsychotics.

Conventional antipsychotics can further reduce cognitive function, which is already impaired in most patients with schizophrenia due to a reduction in dopamine activity in the prefrontal cortex. Anticholinergic drugs used to treat extrapyramidal syndromes or antipsychotics with anticholinergic activity also impair cognitive function. Atypical serotonin-dopamine antagonists have less adverse effects on cognitive function than conventional antidopaminergic antipsychotics and they also reduce the need to use anticholinergic drugs [6].

Remoxipride, which had been available since 1984, has been withdrawn from the market due to adverse effects of aplastic anaemia, but it is still available for compassionate use in some patients. Sertindole has been restricted in some countries due to its cardiotoxicity. In 1998, Lundbeck Ltd., the manufacturers of sertindole, voluntarily suspended the availability of

Table 1: Atypical antipsychotics used for the treatment of schizophrenia. © Jain PharmaBiotech.

Drug	Company/trade name	Comments
Clozapine	Novartis' Clozaril™ or Leponex™	This was the first atypical antipsychotic. It shows greater affinity for 5-HT_{1C} and 5-HT_2 receptors than other receptors. It is associated with agranulocytosis in about 1% of the patients
Olanzapine	Eli Lilly's Zyprex™	The receptor affinity of this drug is similar to that of clozapine, but it has more potent anticholinergic effects
Risperidone	Janssen's Risperdal™	This is a dual 5-HT_2 and dopamine receptor antagonist
Sertindole	Lundbeck/Abbott's Serdolect™	It has β1 adrenergic blocking activity, which may cause hypotension. It is associated with prolongation of cardiac conduction. Withdrawn pending safety reassessment
Quetiapine	Zeneca's Seroquel™	This is considered to be more selective for 5-HT_2 receptors than D_2 receptors
Zotepine	Fujisawa	It is a dopamine antagonist and claimed to be particularly effective for negative symptoms. Available only in Japan and a few European countries

the drug due to concerns about cardiac arrhythmia and sudden cardiac death associated with its use. Sertindole was therefore withdrawn from the market pending discussion with the European Regulatory Authority over cardiac safety.

Clozapine still remains the most widely prescribed atypical antipsychotic agent. According to the Cochrane Database of Systematic Reviews, the equal effectiveness and tolerability of new atypical drugs in comparison with clozapine has not been proven as yet [7].

New drugs are usually started at as low a dose as possible and then increased over several weeks in response to changes in symptoms and side effects. Treatment is usually continued for one to two years. Those patients who have had only one acute psychotic episode and who have had a good response to drug treatment may be suitable for a trial of time without drug treatment. For those patients who have had two or more acute episodes, treatment is continued for at least five years.

3. Overview of the market

Schizophrenia affects about 1% of the general population and imposes a huge financial burden on society. It affects more than 2 million people in the US alone and of these about 330,000 are hospitalised each year because of this disease. At any given time, more than half of schizophrenic patients are under some form of treatment. In the US, the cost of care for schizophrenia exceeds US$ 85 billion per year in direct as well as indirect costs [8]. Financial rewards for improved drugs for the treatment will be considerable. Worldwide market for atypical antipsychotics, which is expected to be US$ 1.5 billion in the year 2000 (about half of the total antipsychotic market of US$ 3 billion), will cross the US$ 3 billion mark by the year 2005, when the total antipsychotic market will be about US$ 5 billion [8].

Conventional antipsychotics still constitute a major portion of the antipsychotic drug market worldwide. During the past few years, most of market for atypical psychotics was held by clozapine, but it is now being shared by several new entries. In calculating the market size for antipsychotics, one should consider that schizophrenia comprises only about 38% of it. The rest of the market for antipsychotic medications is made up of manic depression (21%), dementia (11%) and other disorders (30%), which include conditions such as Tourette's syndrome, aggressive behaviour, mental retardation, personality disorder and psychotic episodes [8]. There is also off-label use. For example, clozapine is used for psychosis of Parkinson's disease. The markets for antipsychotics are thus much bigger than what is anticipated form the number of schizophrenic patients.

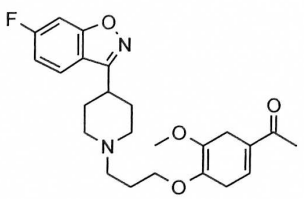
4. Products in development

A selection of the drugs in late stages of clinical development for schizophrenia is shown in **Table 2**. These, along with the atypical antipsychotics in clinical use, will be considered in competitive evaluation of iloperidone.

Table 2: Drugs in late stages of development for schizophrenia. © Jain PharmaBiotech.

Drug	Company	Mode of action	Status
Amisulpride	Sanofi-Synthelabo	Selective antagonist of D_2 and D_3	Available in some European countries and awaiting registration in others
Iloperidone (Zomaril™)	Novartis	Inhibits both dopamine and serotonin receptors	Phase III
SR-46349	Sanofi-Synthelabo	5-HT_2 receptor antagonist	Phase IIb
M-100907	Aventis	Selective 5-HT_2 receptor antagonist	Phase III
ORG-5222	Organon	A combined a 5-HT_{2A}, D_2 and α_1 receptor antagonist	Phase II
Ziprasidone (Zeldox™)	Pfizer	Blocks 5-HT_{2A}, 5-HT_{2C} and 5-HT_{1D} receptors as well as D_2 receptors	Approval recommended by the US FDA in July 2000. Launched in Sweden in September 2000

Figure 1: Structural formula of iloperidone.



Some of the ideal properties of an atypical antipsychotic that should be taken into evaluation of a new drug are:

- Effect on both positive as well as negative symptoms of schizophrenia
- Should not produce any movement disorders such as extrapyramidal syndromes and tardive dyskinesia
- Good safety and tolerability profile, particularly with regard to the cardiovascular and haemopoietic systems
- Should not produce impairment of cognitive function
- No gain of weight as a side effect
- Should not raise prolactin levels
- Cost-effectiveness
- Improvement of the quality of life

5. Details of the drug

Iloperidone, a benzisoxazole, was originally developed for schizophrenia by Hoechst Marion Roussel (now Aventis), who filed for a European patent for this drug in 1990 and started Phase I clinical trials in 1995. Hoechst Marion Roussel licensed it to Titan Pharmaceuticals in 1997. In 1998, Novartis made a deal for worldwide development (except Japan) of iloperidone with Titan and is conducting Phase III clinical trials. Novartis predicts a filing in 2001, with a possible launch in 2002.

5.1 Chemistry

Iloperidone is a mixed 5-HT_{2A}/D_2 antagonist. Its chemical name is 1-(4-(3-(4-(6-fluoro-1,2- benzisoxazol-3-yl)piperidinyl)propoxy)-3-methoxyphenyl) ethanone and its structural formula is shown in **Figure 1**. Iloperidone does not have the tricyclic structure of other atypical neuroleptics such as olanzapine, clozapine and quetiapine, but it is structurally related to risperidone. It was selected for further development because of its greater affinity for the 5-HT_2 over D_2 receptors.

Synonyms of iloperidone are as follows:

- HP-873 (research code)
- ILO-522 (research code)
- Zomaril™(trade name, Novartis)

5.2 Pharmacology

5.2.1 Pharmacodynamics

Although the action of atypical antipsychotic agents has been ascribed to 5-HT_2/dopamine D_2 antagonism, the exact pharmacological mechanism underlying the efficacy is unknown. Most of the atypical antipsychotics also block serotonin, adrenergic, histamine and acetylcholine receptors, which may be involved in the antipsychotic effect. A study of dopa

Table 3: *In vitro* and *ex vivo* studies of pharmacology of iloperidone.

Effect studied	Experimental model	Results	Ref.
[3H]spiperone displacement	Rat frontal cortex and striatum	High affinity for the 5-HT_2 over D_2 receptor	[13]
Dopamine/5-HT receptor affinity	Rat frontal cortex and striatum	High affinity for the 5-HT_2 over D_2 receptor	[12]
Affinity of iloperidone to a variety of human and rat homologues of dopamine and 5-HT receptor subtypes	Receptor binding assays using membranes from cells stably expressing human dopamine D_1, D_{2S}, D_{2L}, D_3, D_4 and D_5 and 5-HT_{2A} and 5-HT_{2C} receptors and rat 5-HT_6 and 5-HT_7 receptors	Iloperidone displayed higher affinity for the D_3 receptor than for the D_4 receptor. Iloperidone displayed high affinity for the 5-HT_6 and 5-HT_7 and was found to have higher affinity for the 5-HT_{2A} than for the 5-HT_{2C} receptor	[20]
Binding of [3H]spiperone to receptors	*Ex vivo* receptor autoradiography studies	Pretreatment with iloperidone inhibited the binding of [3H]spiperone to cortical and subcortical 5-HT_2 receptors by 42 - 94%, in contrast to only 1 - 15% inhibition of [3H]spiperone binding to D_2 receptors in the nucleus accumbens and striatum	[9]

accumulation in the brain as an index of dopamine turnover in response to D_2 receptor blockade has shown that iloperidone is a 5-HT and dopamine receptor antagonist with weak activity at presynaptic dopamine autoreceptors [9]. Iloperidone displays high affinity for α_1, D_3 and 5-HT_{2A} receptors, moderate affinity for D_1, D_2, α_{2C} and 5-HT_{1A} receptors and low affinity for α_{2A}, 5-HT_{2C}, histaminic H_1 and muscarinic M_1 receptors [10]. Antagonism of D_3, α_{2C} and 5-HT_{2A} can lead to increase of dopamine and glutamate release in the frontal cortex. In conclusion, iloperidone displays targeted modulation of multiple neurotransmitter systems including dopaminergic, noradrenergic, serotonergic and possibly glutamatergic effects. These explain the efficacy of iloperidone against positive, negative and cognitive symptoms of schizophrenia with reduced possibility of movement disorders [11]. Low affinity for histaminic H_1 minimises adverse effects such as sedation and seizures, whereas low affinity for muscarinic M_1 receptors is likely to minimise cholinergic adverse effects. Low affinity binding to 5-HT_{2C} receptors correlates with low potential for weight gain.

5.3 Preclinical studies

5.3.1 *In vitro* and *in vivo* studies

The *in vitro* studies are shown in **Table 3**.

Antipsychotic activity of iloperidone has been studied on apomorphine-induced climbing behaviour in mice *in vivo*, which is antagonised by iloperidone [12]. Iloperidone was found to be the most potent of the analogues of iloperidone as compared with haloperidol in antagonising climbing behaviour in mice [13].

5.3.2 Pharmacokinetics

Metabolism of the newer antipsychotic agents has been reviewed elsewhere [14]. Iloperidone is extensively metabolised by rats, dogs and man by a number of metabolic processes, including *O*-dealkylation, hydroxylation and reduction of the acetopheone ring structure with quantitative differences between species [15]. The primary metabolites are further oxidised/conjugated with glycuronic acid. Oxidative *N*-dealkylation also occurs and leads to the formation of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole and the acid derivative of the remaining part of the iloperidone molecule. Other pathways common with risperidone include the opening of benzisothiazole ring, which is apparently mediated by liver enzymes rather than gut flora as postulated for risperidone. In humans, the main circulating metabolite is reduced iloperidone, which is produced mainly by cytosolic enzymes, although CYP1A2, CYP2E1 and CYP3A4 may also play a role [16]. Liquid chromatography/mass spectrometry was used in the initial studies to confirm the identities of the metabolites.

Table 4: Clinical trials of iloperidone.

Trial design	Results and evaluation	Ref.
Phase I study of safety, tolerability and effect of food on the pharmacokinetics of iloperidone in healthy volunteers	Iloperidone was found to be well-tolerated. The adverse effects were less pronounced when it was taken with food	[21]
In a Phase II clinical trial, iloperidone was administered in a fixed dose regimen (4 and 8 mg daily) over a 6-week period after being titrated to maximal dose over 3 - 10 days. Patients included 104 hospitalised men and women with acute or relapsing schizophrenia according. Efficacy and safety were assessed at weekly intervals	All three treatment groups showed improvement from baseline, with iloperidone 8 mg/day reaching statistical significance at end-point	[22]
Phase II prospective, randomised, double-blind, placebo-controlled, flexible dose, parallel group, single-centre study to evaluate the safety, tolerability and efficacy of iloperidone (0.5 - 6 mg/day in two divided doses) compared with placebo in treating psychotic and behavioural symptoms in elderly patients with dementia	Iloperidone, up to and including 6 mg/day, was safe and well-tolerated by elderly patients with psychotic and behavioural symptoms associated with dementia	[23]
Phase III prospective, double-blind, randomised trials with iloperidone are being conducted by Novartis Pharmaceuticals Corporation under the ZEUS (Zomaril™ Efficacy Utility and Safety) programme name. This programme will enrol over 3300 patients in eight Phase III studies at 208 sites in 24 countries. ZEUS is designed to assess the safety and efficacy of three fixed doses of ilioperidone in patients with schizoaffective disorders or schizophrenia	Four of the seven planned trials are ongoing. Efficacy in these trials will be evaluated using Positive and Negative Syndrome Scales, Clinical Global Impression of Improvement Scale, Calgary Depression Scale, Psychotic Anxiety Scale, cognitive function tests and quality of life scales	[24]

In the rat, iloperidone and metabolites were found to penetrate extensively into the brain. Protein binding is 91, 87 and 93% in rat, dog and man, respectively, over the concentration range 5 - 500 ng/ml [17]. The majority of iloperidone administered either orally or intravenously is recovered in the faeces within 24 h, suggesting a biliary excretion as the principle route of elimination.

The pharmacokinetics of iloperidone (3 and 5 mg) were studied in three groups of nine healthy, male volunteers in a placebo-controlled, randomised design. The drug was well-absorbed after oral administration, reaching peak concentration 2 - 3 h after administration of a single dose [18].

5.4 Clinical trials

Clinical trials for safety and efficacy of iloperidone are shown in **Table 4**.

5.5 Drug safety

Iloperidone has undergone extensive toxicology studies (teratogenicity, mutagenicity and carcinogenicity), in which no unexpected adverse findings were observed. In over 300 patients treated with iloperidone prior to the Phase III clinical trials, iloperidone has shown a low incidence of extrapyramidal symptoms and weight gain, problems that effect some of the currently marketed antipsychotic drugs.

In a study using a daily titration schedule of daily dose increases, doses up to 24 mg were found to be well-tolerated [18]. Some of the adverse effects of iloperidone in Phase I clinical trials included dizziness (lasting as long as 7 h in some cases), orthostatic hypotension with syncope, nausea, headache, fatigue, sedation and impaired balance. No clinically relevant changes in any laboratory parameter, physical examination or ECG results were seen. Iloperidone treatment has not been associated with cardiac arrhythmias or liver dysfunction. There was only one case of neutropoenia after administration of iloperidone, but the neutrophil count returned to baseline after three days. In Phase II studies, tolerability in patients was much better compared with the tolerability of the compound in volunteers. This is in keeping with the generally recognised fact that antipsychotic drugs are tolerated better by schizophrenic patients than normal subjects.

5.6 The ReALIZe clinical programme for iloperidone

The ReALIZe (Research to Assess the Long-term Impact of Zomarilx™) programme is a global development undertaking to assess the long-term safety and

efficacy of iloperidone in schizophrenia. This program will involve 3500 patients in 27 countries and 300 physicians. The information from clinical trials will be used, but this programme will also include patients with schizo-affective disorders and drug abuse, who are usually excluded from Phase III clinical trials. A key study in this programme is Study ILP3003 in Latin America [19]. This study will examine the safety and efficacy of iloperidone (4 - 16 mg/day) in comparison with haloperidol (5 - 20 mg/day) in treating patients with psychotic illnesses. The study is designed for 52 weeks, but may be extended by one year where clinically appropriate. So far, 400 patients have been randomised to either iloperidone or haloperidol. There will be intensive safety monitoring of laboratory parameters and electrocardiograms and extrapyramidal syndromes (EPS) ratings will be taken. Assessment will include those for efficacy, cognitive function and quality of life. Finally PET studies will be performed before and after treatment.

6. Concluding remarks and expert opinion

6.1 Safety and efficacy of iloperidone

The receptor affinity profile of iloperidone is similar to the multireceptor affinity type associated with atypical antipsychotics such as clozapine. Its high affinity for the dopamine receptors and various serotonin receptors, however, shows that its profile differs from that of other atypical antipsychotics. Based on the present data, iloperidone is an effective antipsychotic agent. It has been shown to be well-tolerated in human healthy male volunteers as well as patients with schizophrenia and has good oral bioavailability. One of the favourable points for iloperidone is the good safety profile demonstrated so far in clinical trials, low risk of inducing extrapyramidal syndromes and lack of granulocytopoenia.

First data from Phase II trials demonstrated efficacy in patients at doses of 8 mg/day. The minimal effective dose will be further defined in future trials. Tolerability was good up to 32 mg/day, without clinically relevant extrapyramidal syndromes or other side effects. From the information available to date, iloperidone appears to be a promising atypical antipsychotic agent.

6.2 Competition with other atypical antipsychotic agents

Iloperidone, with a balance of activity at the dopaminergic and serotonergic receptors, has obvious advantages over clozapine and olanzapine both of which have a similar receptor profile as they favour serotonergic over dopamine receptors. The use of clozapine is restricted by the adverse effect of neutropoenia but lack of this adverse effect places iloperidone in a position to be considered as the first-line therapy for schizophrenia. Its safety and tolerability has also been shown in elderly demented people with psychoses.

Sertindole has β_1 adrenergic receptor blocking activity that may cause hypotension. It may produce slowing of QT interval with risk of cardiac arrhythmias and currently, the manufacturer has voluntarily suspended marketing pending further studies. Serotonin receptor antagonists such as SR-46349 (Sanofi-Synthelabo) and M-100907 (Aventis) have the drawbacks of some of the adverse effects of serotonin-modulating drugs including sexual disorders.

Competing agents with dual action include risperidone, quetiapine and ziprasidone. The first two are already in the market, but the last one received an approvable letter from the FDA in July 2000 and may reach the market before the end of 2000. It does not have gain of weight as an adverse effect and shares this feature with iloperidone. This drug may provide marketing competition for iloperidone.

6.3 Limitation of the evaluation and future prospects

One of the limitations of the evaluation of efficacy and effectiveness of newer antipsychotic agents has been the lack of statistical power. This makes it difficult to judge whether newer drugs are more effective, less effective or equivalent to clozapine [7]. Trials of sufficient power, with longer duration, measuring clinically important outcomes, are required to assess the true comparative clinical effectiveness, tolerability and cost effectiveness of more recent drugs in relation to clozapine. In the case of iloperidone, the number of patients anticipated to be involved in clinical trials is 3300, which should provide adequate statistical power for the evaluation of results once the trials are completed. Moreover, the rigorous design of the studies and global research to assess the long-term efficacy and safety of iloperidone are reasons for

optimism for reliable results of treatment of schizophrenia and other psychoses with iloperidone.

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Kewal K Jain
Jain PharmaBiotech, Bläsiring 7, CH-4057 Basel, Switzerland
Tel. & Fax: +4161 692 4461;
E-mail: jain@pharmabiotech.ch