SPN809 – Potent Once Daily sNRI for Depression with Associated Sexual Dysfunction

Available for Ex-US Territories

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Clinical and Commercial Opportunity

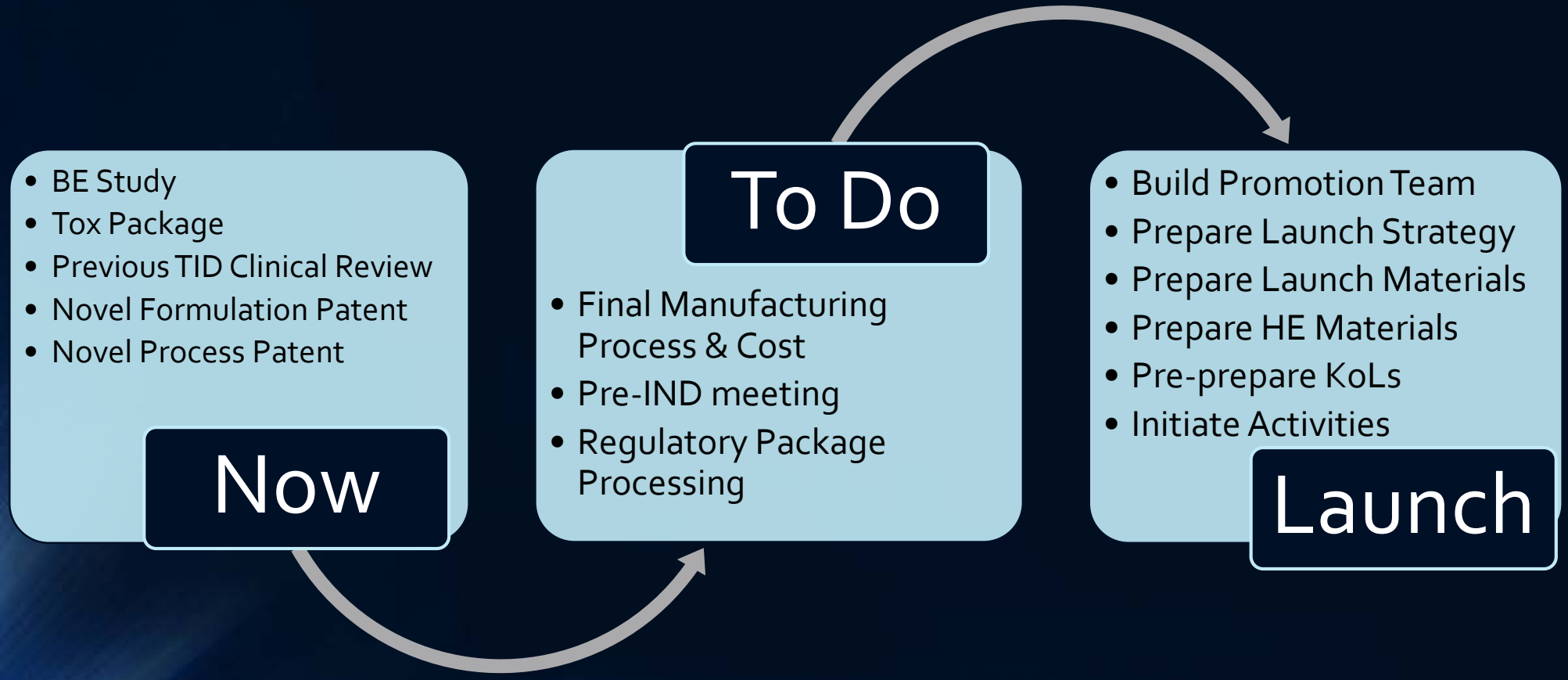
Sections:

- Regulatory Strategy to Re-launch
- Unmet Need in the Depression Market
- Target Product Profile and Positioning
- Health Economic and Pricing Considerations
- Ad Hoc Market Research
- Conclusion

Regulatory Strategy for Re-Launch

- Hybrid/Bibliographic Regulatory Pathway is available in Europe
  - Single Market application proposed starting with UK/Ireland
  - Subsequent Mutual Recognition option is available for selected European countries
- Single Market License can be used in selected other territories and can be taken by local companies
- Where required by regulatory authorities, further local clinical trials will have to be supported by local companies
- Where required secondary packaging can take place locally

Regulatory through to Commercialisation



Identifying Unmet Need in the Depression Market
Current Treatment:

- NICE Guidelines
  - First Line - generic SSRIs
  - Second Line – venlafaxine/duloxetine or TCAs
  - Specialist only – MAOIs
  - Third Line – Vortioxetine (Brintillex) – causes sexual dysfunction, no additional efficacy benefit over SSRIs
  - Not recommended – Agomelatine – lack of demonstrated efficacy

SSRIs Dominate

'SSRIs are a plaster cast over the symptoms allowing CBT to get to work at resolving the situation'

Prof Allan Young (Mood Disorders, Institute of Psychiatry)

Identifying Unmet Need in the Depression Market
Shortcomings of SSRIs:

- Sense of 'Clouded World'
- Sexual Dysfunction with Unipolar Depression estimates range from 25-47% (1)
- SSRI induced sexual dysfunction estimates range up to 80% but variability in individual sexuality and baseline levels makes this almost impossible to validate (2)
- SSRIs are associated with increased suicide ideation
- SSRIs can cause withdrawal discomfort

1. Baldwin DS: Depression and sexual function. J Psychopharmacol 1996; 10(suppl 1):30–34
2. Montgomery SA, Baldwin DS, Riley A: Antidepressant medications: a review of the evidence for drug-induced sexual dysfunction. J Affect Disord 2002; 69:119–140

Sexual Dysfunction Issues

TABLE: Management Strategies for SSRI-Associated Sexual Dysfunction

1. Start with an antidepressant that is not associated with sexual dysfunction. Rothschild suggested that starting treatment with bupropion, mirtazapine, or nefazodone may be a useful strategy for sexually active patients.
2. Switch to an antidepressant that has a lower incidence of sexual dysfunction. Several studies have documented the usefulness of switching to an antidepressant with a lower incidence of sexual dysfunction, such as bupropion, mirtazapine, and nefazodone. This strategy may work with some patients, but it may be difficult to implement in cases where several other antidepressants have been tried and the offending agent is the only one that has been helpful in alleviating depression.
3. Wait for spontaneous remission of dysfunction or for tolerance to develop. This approach may require a long wait, which is not always acceptable to the patient; the effectiveness of this strategy is low.
4. Reduce the dose of antidepressant to the minimal effective dose. With some antidepressants, associated sexual dysfunction seems to be dose dependent, and decreasing the dose might be helpful. However, this approach requires careful, continuous assessment of depressive symptoms, as depression may recur after the dose is lowered.
5. Introduce drug holidays or partial drug holidays. The antidepressant can be discontinued (holiday) or the dose decreased (partial holiday) for a brief period (e.g., 2–3 days), with sexual activity scheduled at the end of the period. In one study (32), this approach was found to be successful with shorter-half-life SSRIs such as paroxetine and sertraline but not with fluoxetine. This approach carries risks, however, as withdrawal symptoms may occur, anxiety may worsen, and nonadherence may be encouraged.
6. Suggest that sexual activity be scheduled around the daily dose of antidepressant, so that sexual activity occurs just before the patient takes the entire daily dose of the antidepressant. The evidence of efficacy for this strategy is limited. It may work with some short-half-life antidepressants.
7. Add "antidotes" or "augmenting" agents. Numerous antidotes or augmenting agents have been described as useful in alleviating SSRI-associated sexual dysfunction. Although most of the literature consists of case reports, results of several studies of the efficacy of such agents have been reported (see reference 33 for a critical review). The following is a partial list of agents that have been reported to be useful: amantadine, bethanechol, bromocriptine, bupropion, cyproheptadine, dextroamphetamine, ginkgo biloba, granisetron, loratadine, methylphenidate, mianserin (not available in the U.S.), mirtazapine, nefazodone, neostigmine, pemoline, pramipexole, ropinirole, sildenafil, tadalafil, trazodone, vardenafil, and yohimbine. a Adapted from Segraves and Balon (22)

Ref. SSRI-Associated Sexual Dysfunction, Richard Ballon MD, Am j Psych 163:9 Sept 2006

Issues with Non-Sexual Dysfunction Anti-depressants

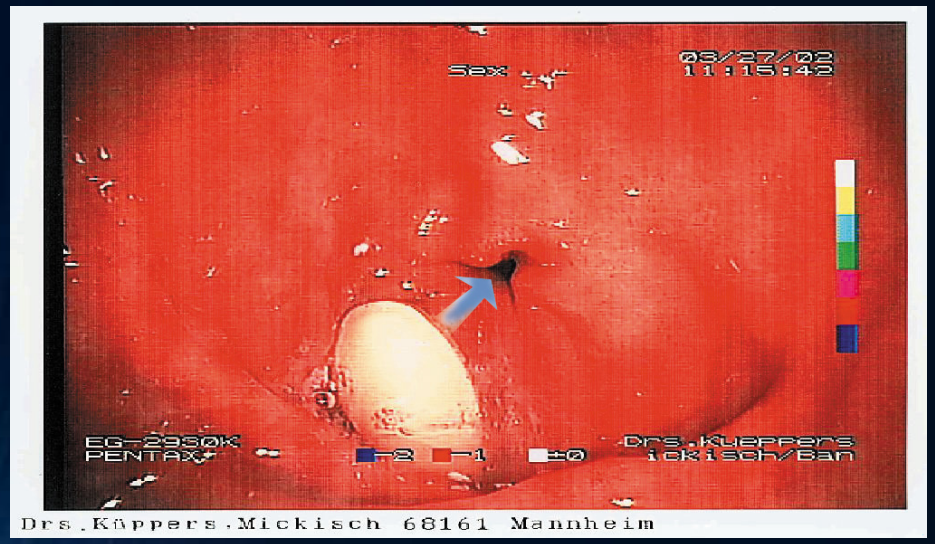
- Buproprion – lack of efficacy
- Mirtazapine – weight gain, interacts with other anti-depressants, can cause hypotension
- Nefazodone – hepatotoxicity in 1 in 250,000 cases lead to withdraw of main brand, generics still available

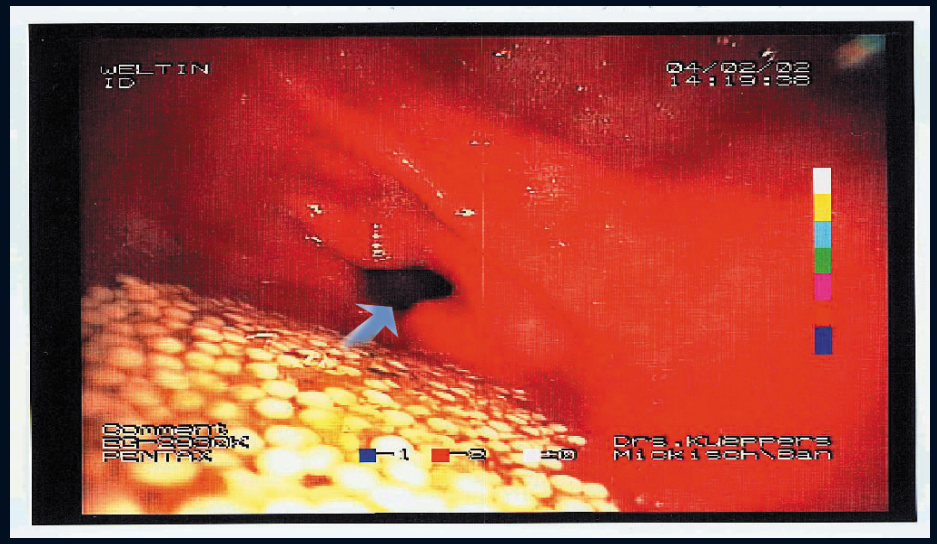
None treat sexual dysfunction associated with depression, they simply don't cause further deterioration of an already reduced level of activity

ViveXiR™ - Target Product Profile and Positioning

- **… test-retest assessments showed a significant improvement of depression and an increase in libido and sex drive…**De Leo D, Magni G, Pavan L.Int J Clin Pharmacol Ther Toxicol. 1983
- **… with SSRIs in particular impaired functions of orgasm and ejaculation can be observed … viloxazine … appears to possess marked stimulating effects on libido and erectile functions …**Hoffman-La Roche AG, Grenzach-Wyhlem, Fortschr Neurol Psychiatry, 1994
- **… double-blind study shows that viloxazine, an atypical antidepressant, could act specifically on sex drive …**Chebili S, Abaoub A, Mezouane B, Le Goff JF; Encephale, 1998
- **… viloxazine proved to have a considerable disinhibiting effect, whose principal expression level was a return to pre-depression levels of frequency in sexual relations …**De Leo D, Magni G.; Br J Psychiatry. 1986
- **… the satisfactory antidepressant activity and the good tolerability of viloxazine in elderly depressed patients make this drug particularly suitable for using in ambulant geriatric depressed patients …A**ltamura AC, Mauri MC, Guercetti G; Prog Neuropsychopharmacol Biol Psychiatry. 1986
- **… tolerance of viloxazine was superior to imipramine …**Poldinger W.; Dtsch Med Wochenschr. 1982

ViveXiR™ – Multi-particle Capsule Benefits





- Sticks on Stomach wall – can irritate causing pain, nausea and vomiting
- Can cause virtual or actual ulceration
- May take considerable time passing through stomach
- Unreliable drug distribution to the blood

- Stays in Lumen
- No Gastric Irritation
- No Nausea & Vomiting
- More reliable Small intestine Delivery
- More reliable Small intestine Absorption

ViveXiR™ Shortcomings

- Vomiting and Nausea due to dose dumping
- This is greatly reduced with the new Once Daily controlled release formulation

The European Medicines Agency (EMA) has acknowledged the inappropriateness of these single-unit, non-disintegrating formulations as agents of choice:

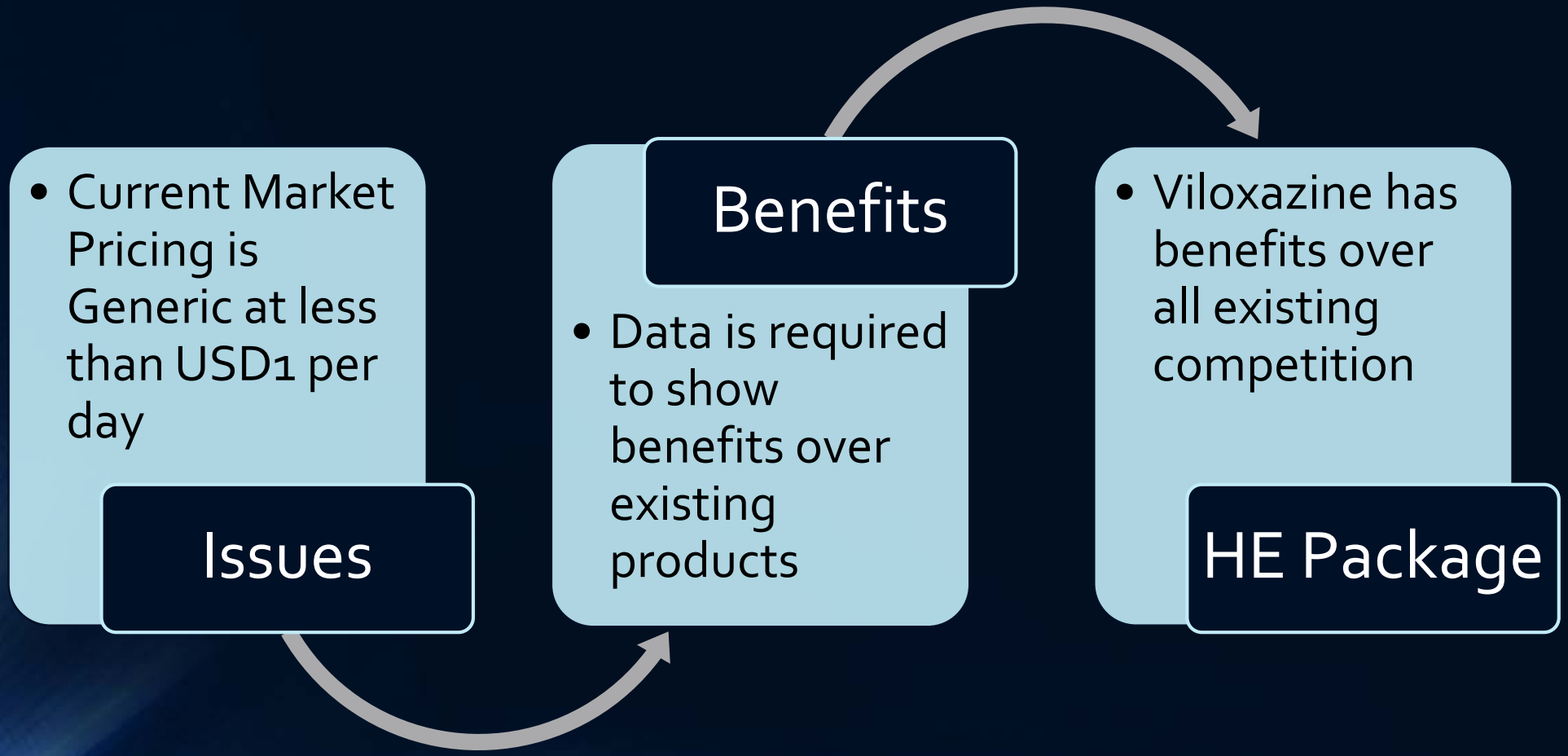
" The development of single unit non-disintegrating dosage forms is discouraged since their residence time in the stomach is unpredictable and in general longer than disintegrating dosage forms with multiple units or pellets. Therefore, such single unit non-disintegrating dosage forms are liable to a higher risk of dosage-dumping "

The implication being that multiple-unit tablet formulations, like that proposed for ViveXiRTM™, improve tolerability and patient compliance.

ViveXiR^{TM} New Target Product Profile

- A potent Nor Adrenaline Reuptake Inhibitor and milder Serotonin Reuptake Inhibitor, Viloxazine appears to be most efficacious against depressive symptoms and not so suitable for the anxiety end of the patient spectrum.
- It has a positive effect on depressed patients' libido and sexual function.
- It appears also to be a useful treatment for narcolepsy.
- It appears to be a suitable agent for severe depression and the elderly and may be of use for other patient types that have been hinted at (eg. drug dependency, ADHD…).
- Side effects are few, with the slow release formulation - levels of nausea and vomiting are reduced dramatically by a reduction in peak concentrations of Viloxazine and by a lack of irritation of the gastric lining. Levels are similar to other antidepressants such as Venlafaxine/Citalopram.
- Interactions with other agents are slight and manageable.

Health Economic and Pricing Considerations



HE Benefit Package

- Proposed Place in Treatment Paradigm – second line usage
- HE Model to demonstrate second line benefit where sexual dysfunction is an issue
- Backup Publications demostrating extent of sexual dysfunction as an issue
- Backup Publications demonstrating ViveXiR™ benefits to libido

Ad hoc Market Research

- 60 European psychiatrists attending CINP
- Office & Hospital Based Prescribing Decision Makers

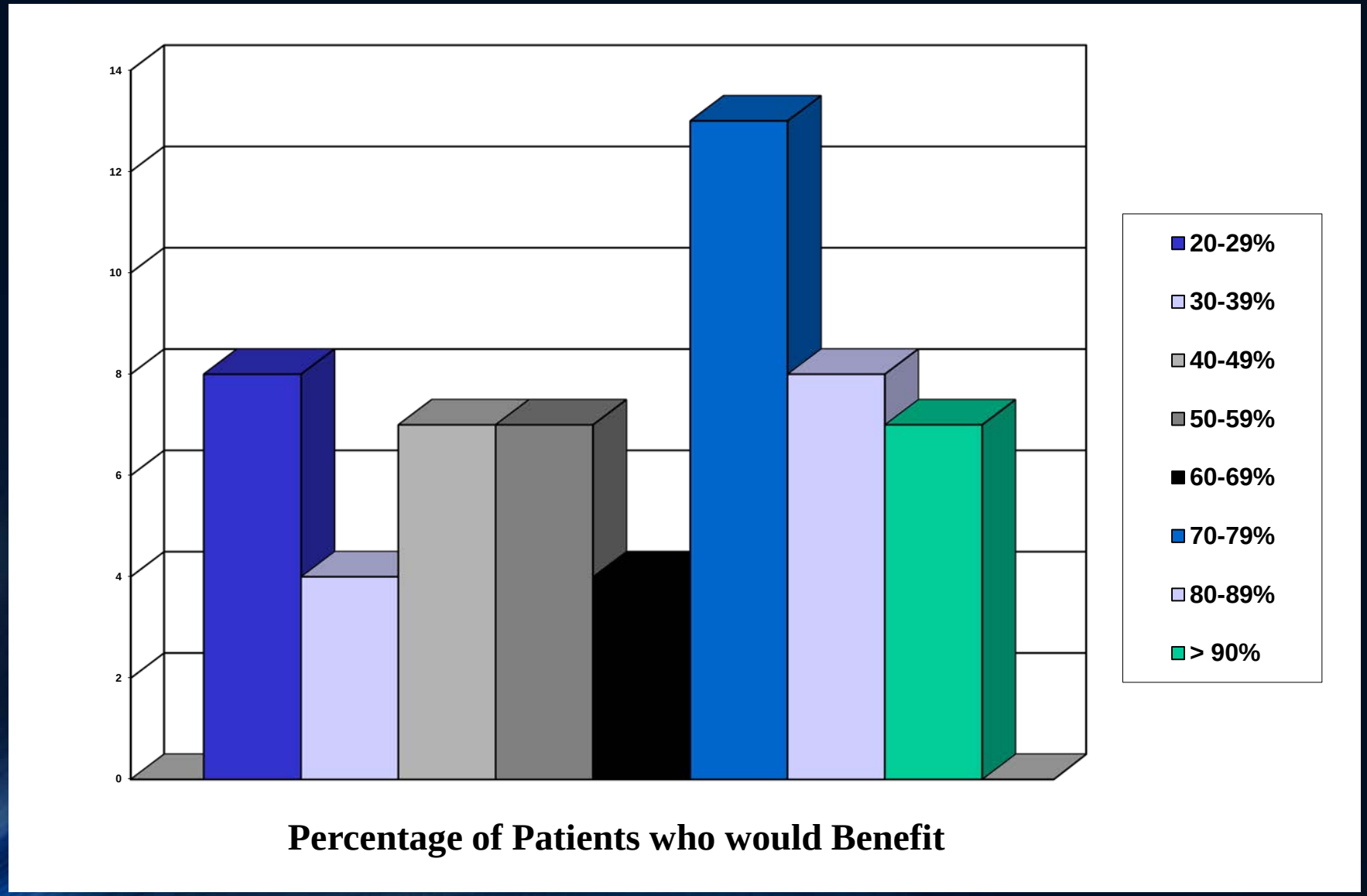
Ad hoc Market Research – Product X Profile

Attribute	Venlafaxine	Duloxetine	Buproprion	Reboxetine	Sertraline	Citalopram S	Paroxetine CR		Product X
Efficacy Depression	+ + +	+ + +	+	+	+ +	+ +	+ +		+ + +
Efficacy Anxiety	+ + +	+ + +	0	+	+ +	+ +	+ +		+
Efficacy in All Patient Types	+ + +	+ + +	-	-	-	-	-		+ +
Headache	- -	- -	-	-	-	-	-		-
Nausea	-	-	-	-	-	-	-		-
Sexual Dysfunction	- -	- -	0	0	- - -	- - -	- - -		+ + +
Dosing	+ +	+ +	+ +	+ +	+ +	+ +	+ +		+ +
Suicide Ideation	+	+	+	+	-	-	- -		+
Cost	- -	- - -	-	-		-	-		-
Withdrawal Symptoms	-	-	0	0	-	-	- - -		0

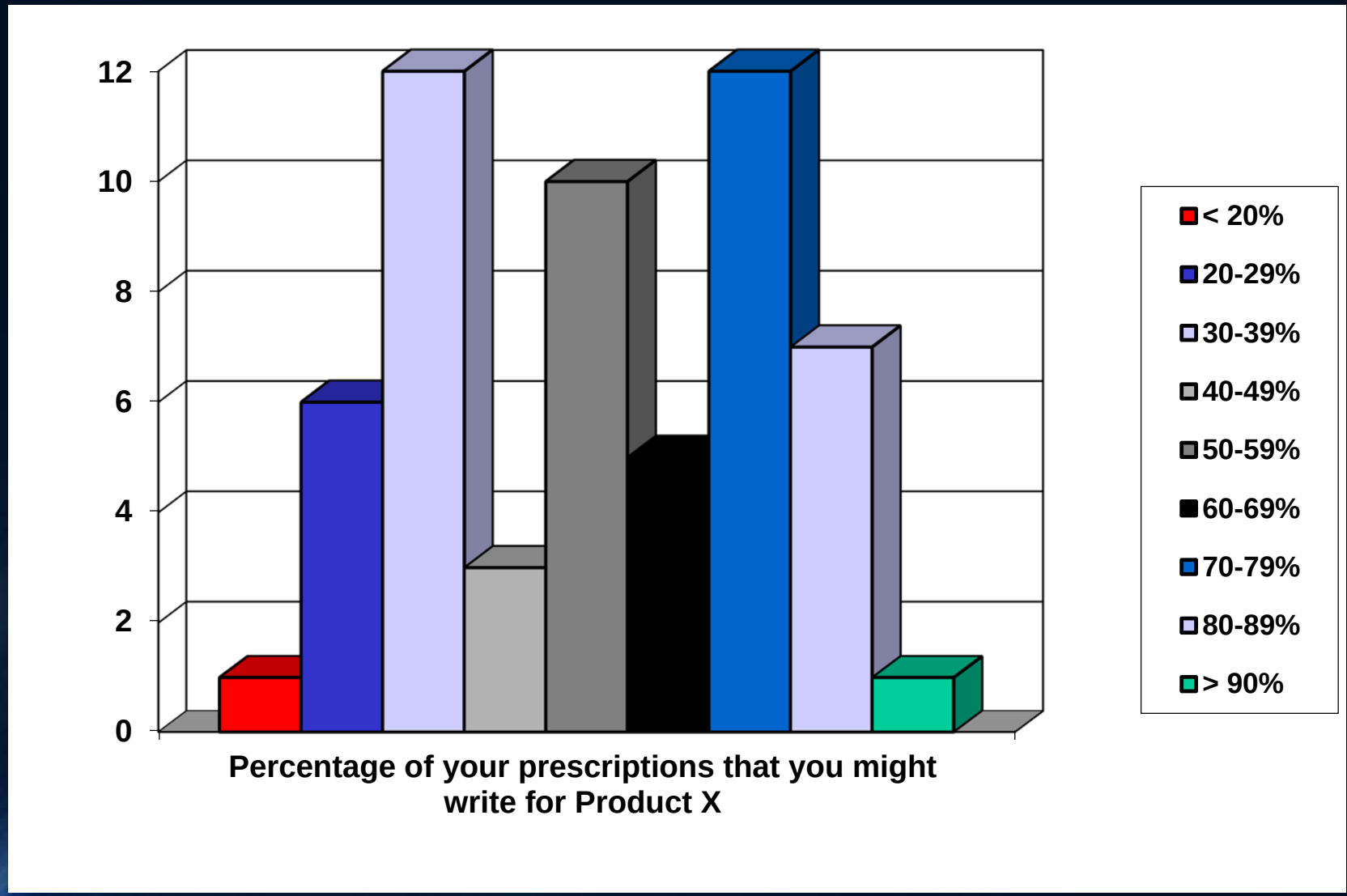
Ad hoc Market Research – Football Scores

• **Product X (ViveXiR™)**	**106**	**vs**	**89**	**Venlafaxine**
• **Product X (ViveXiR™)**	**137**	**vs**	**72**	**Citalopram S**
• **Product X (ViveXiR™)**	**147**	**vs**	**36**	**Reboxetine**
• **Product X (ViveXiR™)**	**166**	**vs**	**52**	**Buproprion**

Ad hoc Market Research



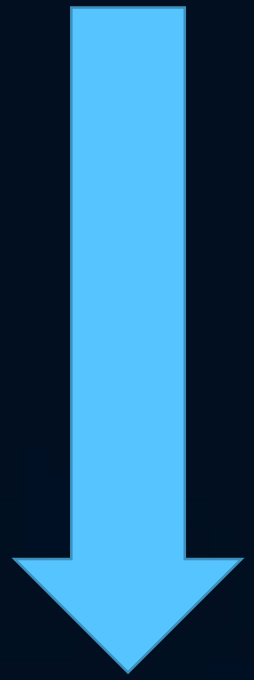
Ad Hoc Market Research



Attribute Ranking & Rating

- Importance
- Efficacy in maintenance
- Efficacy in depression
- Efficacy in severe
- Suicide ideation
- Sexual dysfunction
- Weight gain
- Cost
- Nausea
- Withdrawal symptoms
- Headache
- Dosing
- Efficacy in anxiety

Most important

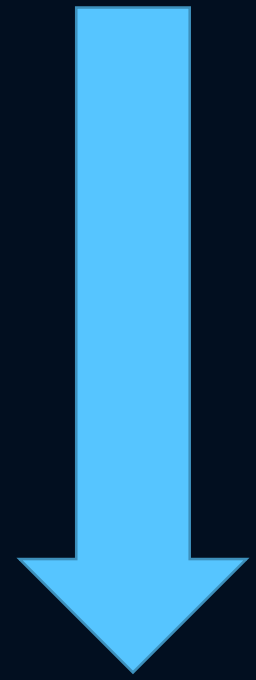


Least important

Satisfaction

Efficacy in maintenance
Dosing
Efficacy in depression
Efficacy in severe
Efficacy in anxiety
Suicide ideation
Headache
Withdrawal symptoms
Cost
Nausea
Sexual dysfunction
Weight gain

Most Satisfied



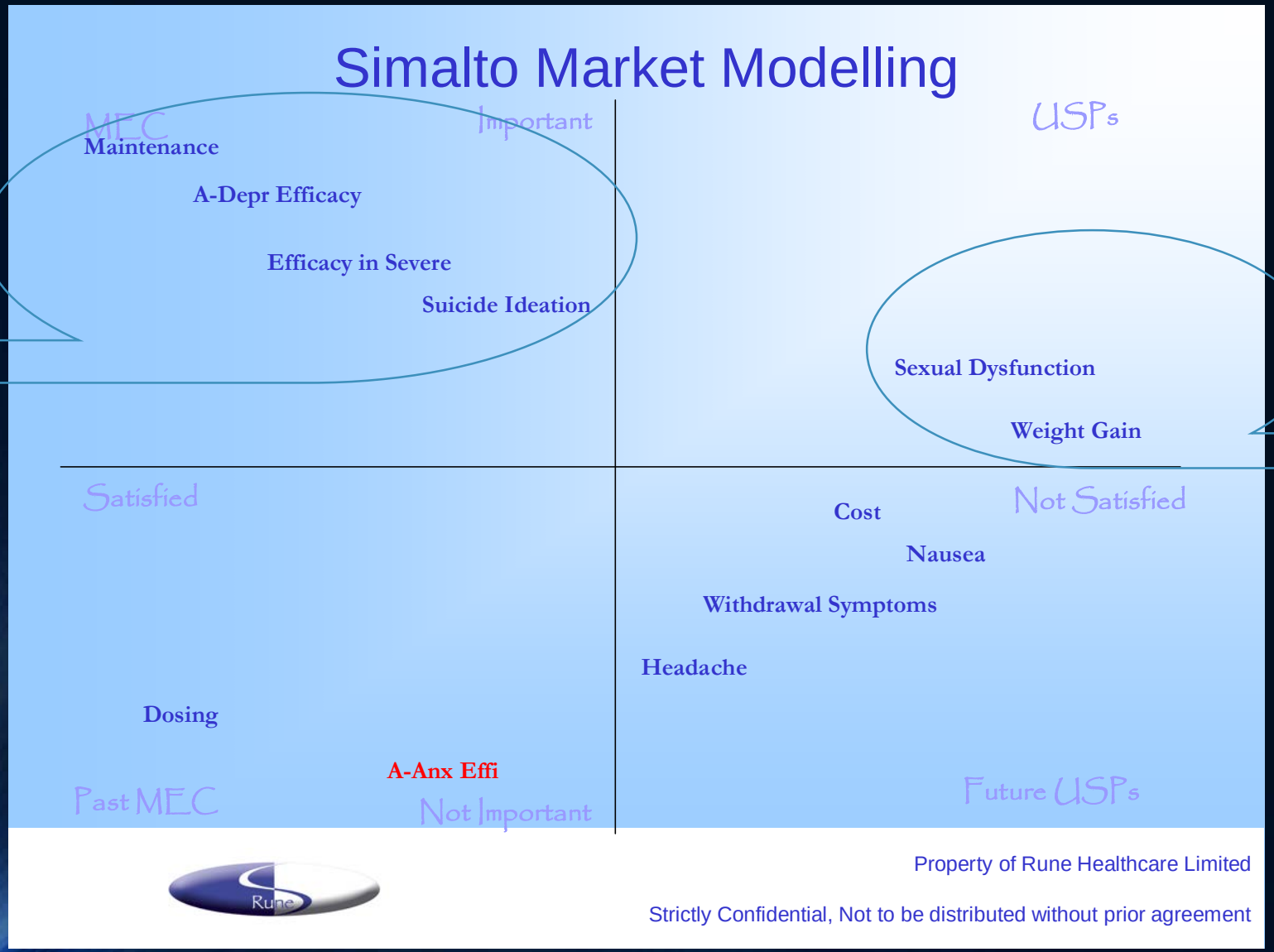
Least Satisfied

Ad Hoc Market Research

Attribute	Current Performance	Unmet Need?
Short term efficacy	1-4 weeks	Yes
Long term efficacy	No 'waning' of effect	No
Cognitive Dysfunction	Sometimes apparent	Yes/No
Effective in Anxiety	Yes	No
Side effects	Noticeable	Yes
Sexual Dysfunction	Noticeable with SSRIs	Yes
Sedation	Sometimes apparent	Yes/No
Suicide Ideation	Evidence Increasing	Yes
Withdrawal symptoms	Present – especially with Paroxetine	Yes
Relapse Prevention	Most patients relapse after drug treatment	Yes
Dosing/Posology	Tablets/Capsules	No
Dosing/Posology	One per day or Less	No
Dosing/Posology	Alternative formulations rare	Yes
Cost	Venlafaxine is not considered expensive	No

Ad Hoc Market Research

Any new product needs to achieve the current market levels of these attributes simply to enter the market successfully (cf. current failures of agomelatine and vortioxetine)



Viloxazine is the only product with libido enhancement as its USP

MEC= Market Entry Criteria
USP= Unique Selling Point

Ad Hoc Market Research

Market Modelling	
Drug	Preference share
Venlafaxine	12.85
Duloxetine	12.85
ViveXiR™	12.49
Sertraline	10.92
Citalopram S	10.70
Fluoxetine OW	10.61
Paroxetine	10.18
Reboxetine	9.89
Buproprion	9.52

Market Research Suggests high preference for ViveXiRTM™, supported by achievements of existing products – the market modelling is reliable

Conclusion

- ✓ The Depression market is currently segmented
- ✓ Opportunities exist to target specific segments and achieve good sales
- ❖ The market is not satisfied with performance of existing products
- ❖ Pricing is currently low
- ✓ An agent with a true USP can command a higher price and succeed
- ❖ ViveXiR™ has a USP BUT past weaknesses offset this
- ✓ A new Once Daily ViveXiR™ with refined drug delivery shows potential
- ✓ ViveXiR™ has been created along with strong new IP
- ✓ Reliable Market Research suggest a good preference share for ViveXiR™
- ✓ ViveXiR™ only requires Regulatory Processing in Europe to be Launch Ready