Fact Sheet – Overactive Bladder

There are around 50 million OAB patients in the USA alone and over 200 million worldwide. The market for drugs in this area is expected to reach $4 billion in 2008. The mainstay of current therapy for OAB is the antimuscarinic class of drugs, however, these compounds have a poor side-effect profile (dry mouth, constipation, CNS issues) and modest efficacy.

OAB is defined by the International Continence Society as a syndrome characterised by urinary frequency, urinary urgency, and nocturia. The symptoms of OAB often arise from instability in the activity, and responses to stimulation, of the bladder muscle (the detrusor), resulting in involuntary contractions of the detrusor during the filling phase. This instability has been attributed to neurogenic (changes in nerve activity) or myogenic (changes in muscle tone or responses) mechanisms. Thus drugs that alter afferent or efferent nerve signals at the bladder, and/or alter the tone of the detrusor muscle are thought to have potential in the treatment of OAB.

There continues to be an interest in the development of new drugs for OAB, and the market is certainly keen to have drugs with a new mechanism of action and an improved side-effect profile. To address this unmet medical need, Xention is developing novel agents for OAB with a much improved efficacy and safety profile that:

- demonstrate clinical efficacy in OAB patients
- have a once or twice daily dosing regimen
- are safe and well-tolerated when administered chronically
- ideally have a beneficial effect on poorly addressed symptoms such as feelings of urgency

TRPV1 as a Target for OAB

Our lead compound for OAB is XEN-D0501, a TRPV1 antagonist. Several studies have characterised the presence and role of TRPV1 receptors in the detrusor muscle and the nerves that innervate the detrusor. In particular, the thinly myelinated Ad fibres and the sensory unmyelinated C fibres have been shown to be modulated by TRPV1 agonists and antagonists. Intravesicular capsaicin, and its more potent analogue res-iberatoxin (both TRPV1 agonists) have been shown to reduce the symptoms of OAB by desensitising these receptors. The normal micturition reflex is governed by afferent fibers comprising mainly Ad nerves, whereas in patients with OAB there is an increased role for C-fibers in the reflex. As TRPV1 receptors are expressed on the endings of these nerves they play an increased role in promoting the reflex to urinate by controlling release of neurotransmitters from spinal nerve terminals. TRPV1 antagonists are expected to suppress the over-active bladder reflexes associated with incontinence.

XEN-D0501 is a highly potent antagonist of TRPV1 and has been studied in several models of OAB in the rat and the dog. XEN-D0501 was found to reduce the intensity of capsaicin-induced bladder contractions in the rat (left panel, below) and dog (right panel).
Fact Sheet – Overactive Bladder

Furthermore, XEN-D0501 was found to extend the interval between bladder contractions induced by distension, in the rat, without reducing contraction amplitude; a preferred combination of effects for the treatment of OAB.

XEN-D0501 has completed a comprehensive pre-clinical safety programme and been found to be safe, well tolerated, and suitable for clinical development. The compound has progressed into clinical safety assessments and single and multiple ascending dose studies have now been carried out. A bioequivalence study will be completed during 2009 to characterise a solid dose formulation, before progression into Phase 2a efficacy studies.