CLX-118

CLX-118: A NOVEL MOLECULAR CONJUGATE OF DICLOFENAC AND EICOSAPENTAENOIC ACID FOR THE MANAGEMENT OF PAIN

- A novel pro-drug conjugate of Diclofenac and Eicosapentaenoic acid (EPA)
- Designed to be stable in the gastric fluid
- Designed to release the active moiety by host enzyme mediated hydrolysis
- Safer than the marketed diclofenac formulations
- Expected to have beneficial pharmacokinetic profile, reduction in dose or with enhanced safety and tolerability profile (reducing the local toxicity in stomach and upper small intestine).
- Robust Patent Portfolio

Cellix Bio Private Limited
CIN: U74900AP2014PTC094095
Tel: +91 40 23545946
Fax: +91 40 23545949
Plot No.1177 B, Road No. 56, Jubilee Hills
Hyderabad, India, 500033
www.cellixbio.com

1. Opportunity Overview

CLX-118 is a novel molecular conjugate of diclofenac with Eicosapentaenoic acid (EPA). In this conjugate, diclofenac is chemically linked with EPA utilizing CellixBio's proprietary patented Synergix platform technology. Diclofenac is linked with EPA through a linker. The ester bonds could undergo hydrolytic cleavage by the host hydrolytic enzymes present in the intestinal fluid/epithelium, blood or in liver.

Chronic pain may result from arthritis, cancer, neuropathy, or an infectious process. With chronic pain, a normal lifestyle can be restricted or even impossible to maintain. Chronic discomfort impacts overall quality of life. The prevalence of chronic pain in the United States is difficult to accurately quantify; however, estimates as high as 20% of the total population is affected (Herndon C.M., 2008). Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) of the phenylacetic acid class with anti-inflammatory, analgesic, and antipyretic properties indicated for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and in other pain management. It is one of the most widely prescribed NSAID worldwide (McGettigan et al., 2013). Diclofenac inhibits, cyclooxygenase (COX)-2 enzyme with greater potency (proficiency) than COX-1 as compared to other traditional NSAIDs. Similar to other NSAIDs, diclofenac is also associated with serious dose-dependent gastrointestinal, cardiovascular and renal adverse effects.

Eicosapentaenoic acid (EPA) is approved by US FDA for the treatment of hypertriglyceridemia. EPA is a component of omega 3–fatty acids and is reported to have several beneficial biological effects that include anti-inflammatory, controlling oxidative stress and stabilization of neuronal membranes (Taha A.Y. et al., 2010).

Cellix Bio proprietary technology driven design of CLX-118 would offer a differentiated diclofenac product with incremental benefit in efficacy, safety, tolerability and the patient compliance than the existing diclofenac formulations and products. So far, we have completed biopharmaceutical assessment and a preliminary pharmacokinetic study in rats.

The expected target product profile/differentiation opportunities of CLX-118 include:

- ✓ Stable in gastric fluid
- ✓ Improved pharmacokinetic profile
- ✓ Excellent gastric safety in comparison with diclofenac sodium

2. Market Description

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of therapeutic agents. The drug alone or in combination with other classes of drug, relieve the symptoms across multiple clinical indications, including short and long term pain and in a range of musculoskeletal disorders (McGettigan P and Henry D., 2013). Prevalence for selected chronic pain conditions such as osteoarthritis and rheumatoid arthritis in the United States populations is 16 million and 2.5 million, respectively (Irena Melnikova, Nature Reviews Drug Discovery 9, 589-590 (August 2010)).

Opioid analgesics and NSAIDs will remain as important paradigm in the treatment algorithm for pain and will comprise at least 45% of total sales in the pain market over the next 15 years. The sales of acute pain drugs in the seven major markets will reach $17.4 billion in 2021. Similar to the chronic pain market, opioid analgesics and NSAIDs continue to hold leading market status in the acute pain space; in 2011, their combined sales made up well over half of the total major-market sales in acute pain, a trend that will continue through 2021 (Decision Resources forecast report - Pharmatimes, 2012).

The total world wide sale of diclofenac sodium (Voltaren) was approximately 550 million USD in 2015 (Reference: Novartis Annual report). According to IMS Health, the U.S. sales of diclofenac sodium topical gel (VOLTAREN®) were approximately $413 million, for the 12 months ending January 2016 (Reference: reported by Amneal Pharma). Annual sales of Diclofenac potassium (Cataflam®) in the USA are in excess of $100 million a year (Analysis report by Teva).

3. Unmet Medical Need

NSAID therapy is recommended for acute or chronic pain resulting from various diseases or conditions. Patients taking NSAIDs should be cautioned about adverse effects, which may include gastrointestinal bleeding, renal dysfunction, and blood pressure elevation. Among the NSAIDs diclofenac is one of the most frequently used drugs for the management of pain. A number of diclofenac containing drug products or formulations have been developed since its first introduction to the market with the goal of improving its efficacy, tolerability, and patient convenience. Delayed release and extended release forms of diclofenac sodium were initially developed for the treatment of patients with chronic pain.

Extended-release diclofenac sodium tablets are associated with a lower C_{max}, delayed t_{max} and similar bioavailability compared with enteric-coated tablets (Altman et al., 2015). However, adverse events reported for diclofenac enteric-coated tablets were generally similar to those reported for other NSAIDs. Though the relative risk of serious GI complications with diclofenac was estimated to be low as compared with other NSAIDs, the hazard of developing gastric/duodenal ulcers and upper GI perforation and bleeding was not eliminated with the use of delayed release (enteric coated) or extended-release tablets.

To reduce the risk for serious gastro intestinal adverse events, with long-term use of diclofenac sodium, co-administration of diclofenac along with gastroprotective agents such as prostaglandin analogs or proton pump inhibitors is followed. Endoscopic evaluation of patients with rheumatoid arthritis or osteoarthritis who used NSAIDs continuously over a period of 6 months revealed clinically significant gastroduodenal lesions in 37 % and ulceration in 24 % of cases.

- In a standard diclofenac therapy, patients requiring more relief of pain and inflammation may increase the dose to 200 mg/day (Voltaren XR label). The dose-related risk of thrombotic events, especially following administration of high doses of diclofenac (>150 mg daily), has been documented in observational studies. Because the incidence of AEs is dose dependent, a reduction of the diclofenac dose is

advisable for patients with risk factors for the development of cardiovascular and gastrointestinal adverse events (Altman etal., 2014).

- There is an opportunity for an improved diclofenac therapy, to produce comparable efficacy at reduced doses, aligned with recommendations by health authorities including the FDA and the European Medicines Agency that NSAIDs should be prescribed at the lowest effective dose for the shortest possible duration (Altman et al., 2015). To date, SoluMatrix diclofenac capsules were the only formulation developed with its 18 and 35-mg doses containing 20 % less active ingredient on a molar basis than 25 and 50-mg diclofenac potassium immediate-release tablets, respectively. Based on the cumulative daily dose of 18 mg three times daily, SoluMatrix diclofenac represents the lowest-dose diclofenac option for the systemic treatment of acute pain.

Hence, there is an unmet need in the diclofenac therapy for a drug which can reduce the dosage without compromising efficacy and improve the safety profile with respect to gastro intestinal events.

4. Scientific Rationale

Diclofenac belongs to a group of NSAIDs that inhibit both COX-1 and COX-2 enzymes. The binding of NSAIDs to COX isozymes inhibits the synthesis of prostanoids (i.e.,prostaglandin [PG]-E2, PGD2, PGF2, prostacyclin [PGI2], and thromboxane [TX] A2). PGE2 is the dominant prostanoid produced in inflammation, and the inhibition of its synthesis by NSAIDs is believed to be the main mechanism of the potent analgesic and anti-inflammatory properties of these agents.

EPA, an omega-3 fatty acid and its esters are approved drugs by USFDA. In CLX-118, EPA is used as a molecular partner for diclofenac and both the moieties are linked through a simple ester linkage. The presence of ester bond in CLX-118, would potentially cleave into active diclofenac moiety by host enzyme mediated hydrolysis either in the intestinal fluid or

its epithelium, blood or in liver. The high lipophilicity and enzymatic hydrolysis in the systemic circulation would possibly prevent the interaction of diclofenac with the gastric epithelium and there by could reduce the incidences of causing ulcer. In addition, enzymatic cleavage in the systemic circulation would lead to improved pharmacokinetic profile.

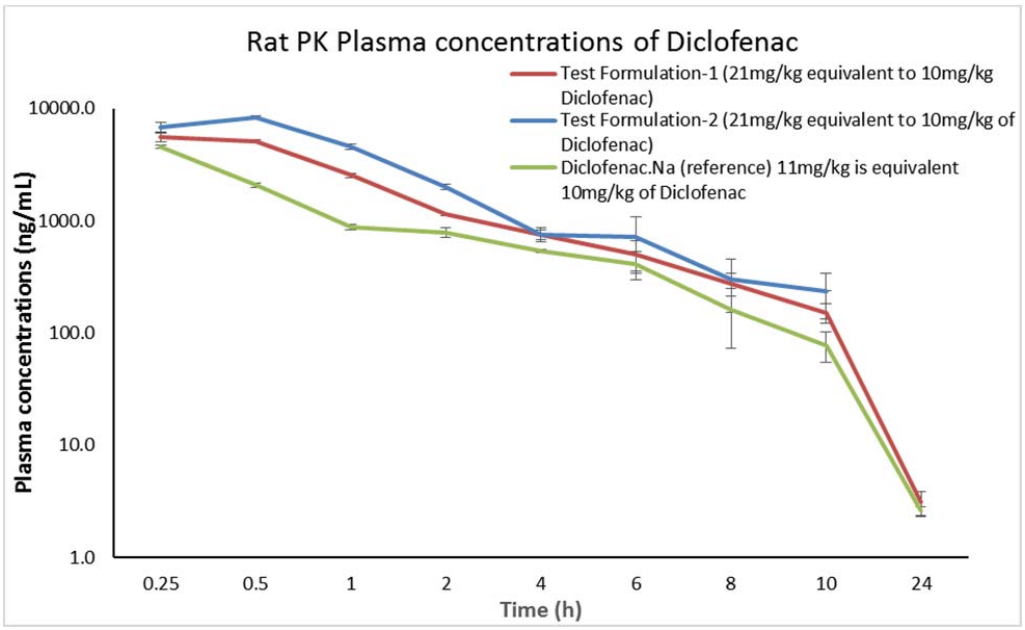
5. Preclinical Summary

Several preclinical investigations were carried out with CLX-118 in order to assess the biopharmaceutical and pharmacokinetic properties.

The biopharmaceutical properties of CLX-118 (solubility, physico-chemical properties and stability in simulated intestinal fluids) are suitable for developing extended release oral dosage form for optimal delivery. Additionally, *in vitro* stability studies using simulated gastric and intestinal fluids, showed that CLX-118 was stable in simulated gastric fluid with pepsin; and 63% the conjugate was degraded in the simulated intestinal fluid with pancreatin.

The comparative pharmacokinetic study of CLX-SYN-G18-C02 (Diclofenac-Eicosapentaenoic acid (EPA) conjugate), and diclofenac sodium after oral administration (dose equivalent to 10 mg/kg diclofenac) to male Sprague-Dawley (SD) rats demonstrated that,

- CLX-SYN-G18-C02 (Diclofenac-EPA conjugate) was below the detectable levels (5 ng/ml) in the plasma samples from the animals dosed with CLX-SYN-G18-C02.
- The plasma C_{max} and AUC_{0-t} of diclofenac was higher (1.2 and 1.6X respectively) in formulation-1 group, when compared with diclofenac sodium alone. There was no change in $T_{max.}$ The relative bioavailability was 160%.
- The plasma C_{max} and AUC_{0-t} of diclofenac was higher (1.8 X and 2.3X respectively) in formulation-2 group, when compared with diclofenac sodium. T_{max} was marginally prolonged in relation to diclofenac sodium group. The relative bioavailability was 234%.



The planned studies include:

- *Demonstration of safety in Ulcerogenicity rat model.*

6. References

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