COMMON TECHNICAL DOCUMENT

MODULE 2.6

NONCLINICAL SUMMARY

FOR THE MEDICINAL PRODUCT HYDROCORTISONE INJ.

(Hydrocortisone Succinate)

PREPARED FOR ……..

By

Expert's signature

Doc. MVDr. Tomáš Sládek, CSc.

Technical Adviser for Pharmaceutical
Industry and Trade

(with expert assistance in literature searching by RNDr. Jarmila Sládková)

MEDEA PHARM s.r.o.

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2.6.1.1 History and critical assessment

"In Nature's infinite book of secrecy a little I can read."

WILLIAM SHAKESPEARE:
Antonius and Cleopatra,
Act I, scene II

THE ADRENAL GLAND was first described by Eustachius in 1563 but its function had been unknown till the clinical description of adrenal insufficiency by English physician Thomas Addison in 1855. Shortly after that, Charles-Édouard Brown-Séquard, one of the most distinguished physiologists of the nineteenth century, showed that surgical removal of the adrenals is lethal to dogs.[1] 36 years later he recalled to these experiments and he tried to keep adrenalectomized animals alive by administering a filtered tissue homogenate of the adrenals with only transient improvement of their moribund state.[1] In 1898 Soddu[2] had noted that the injections of sodium chloride increased the survival of adrenalectomized dogs by hours.

In 1895 Oliver and Schäfer[3] decribed stimulatory physiological effects of aqueous extracts of the whole adrenals on the cardiovascular system of dogs and on isolated hearts. Because the adrenal extracts obtained from patients with Addison's disease had no effects, they erroneosly concluded that this disease resulted from the lack of the substance contained in their extracts. This notion was supported by the fact that Addison's disease is accompanied by low blood pressure. The active principle was subsequently isolated, chemically defined and called epinephrine (adrenaline). Thus at the beginning of the 20th century adrenals had been considered as the organ with the uniform physiological function. In 1910, Arthur Biedl, Professor of General and Experimental Pathology at the German University of Prague, published experiments that had brought the evidence of functional differentiation of the adrenal cortex and medulla.[4, 5] He removed so called interrenal organ in cartilaginous fishes, which had been shown to correspond histologically to the isolated adrenal cortex in mammals, and observed that the animals had died. So he concluded that the cortex not medulla was essential to live.

In the late 1920s and early 1930s, interest in the adrenal cortex, its physiology, and diseases was intense. In the late 1920s, Marine and Baumann[6] and Rogoff and Stewart[7] reported the increased survival of the experimental adrenalectomized animals treated by the injection of Ringer's solution or sodium chloride. Swingle and Pfiffner[8] at Princeton University, USA, were the first to prepare extracts from the adrenal cortex, which partially controlled the symptoms of adrenal insufficiency in adrenalectomized animals. In 1933, Robert Loeb and his associates at Columbia University, USA, have demonstrated[9] that after the adrenal glands of the dogs had been removed for a day or two, the blood began to show a progressive reduction of the sodium chloride content and also plasma volume. On the contrary, the hematocrit and the potassium concentration rise. The animals eventually die of acute renal failure due to circulatory shock.[10] In 1934 Zwemer and Sullivan[11] have shown that this state can be reversed by administration of cortical extract. That the crude suprarenal cortical extract causes a