CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

PHARMACOLOGY REVIEW

NDA 21-272

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

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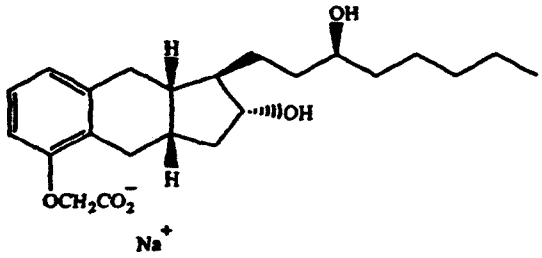
ORIGINAL NDA DATED: August 11, 2000
CENTER RECEIPT DATE: August 14, 2000
REVIEWER RECEIPT DATE: August 15, 2000

SPONSOR: United Therapeutics Corp.
P.O.Box 14186, Research Triangle Park, NC 27709

DRUG PRODUCT: Remodulin Injection

DRUG: Generic name – Treprostinol sodium
Code names – UT-15, 15AU81 and LRX-15



M.W. 412.49

FORMULATION: Remodulin Injection is a sterile sodium salt solution supplied in 20 ml multi-use vials containing 1.0, 2.5, 5.0 or 10.0 mg/ml of treprostinol. Each ml of the formulation also contains 5.3 mg sodium chloride (except for the 10.0 mg/ml concentration which contains 4.0 mg sodium chloride), 3.0 mg metacresol, and 6.3 mg sodium citrate. Sodium hydroxide and hydro-chloric acid are added to adjust the pH between 6.0 and 7.2.

PHARMACOLOGICAL CLASS: Prostacyclin (PGI_2) analog

PROPOSED INDICATION: Treatment of pulmonary arterial hypertension (PAH)

PROPOSED DOSAGE REGIMEN: Remodulin is administered by continuous subcutaneous infusion at an initial infusion rate ≤1.25 ng/kg/min, with upward and downward adjustments based on PAH symptoms and drug-related adverse effects. It is recommended that increments not exceed 1.25 ng/kg/min per week for the first four weeks and 2.5 ng/kg/min per week for the remaining duration of infusion.

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED: .

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SUMMARY OF PHARMACODYNAMIC STUDIES

(The pharmacological data submitted in this new drug application are compiled from studies conducted at the [redacted]

UT-15 (formerly known as 15AU81 or LRX-15), a chemically stable tricyclic benzindene analogue of prostacyclin (PGI_2, epoprostenol), is currently being developed for the treatment of pulmonary arterial hypertension. In vitro and in vivo pharmacodynamic studies have shown that UT-15 possesses systemic and pulmonary vasodilatory and platelet anti-aggregatory properties. These studies are summarized below.

In Vitro Studies Related to Proposed Indication

1. Platelet Antiaggregatory Activity

Rat platelet-rich plasma was incubated with UT-15 at concentrations ranging from 5.1 to 102.4 nM (2-40 ng/ml) for 1 minute at 37°C prior to the addition of ADP (10 µM). UT-15 produced a concentration-dependent inhibition of ADP-induced platelet aggregation (Table 1) with an IC_{50} of 34.6 nM (13.5 ng/ml)

Table 1.

INHIBITION OF PLATELET AGGREGATION IN VITRO IN RAT PLATELET-RICH PLASMA BY UT-15

Concentration (nM)	% Inhibition
5.1	8 ± 5
10.2	12 ± 5
25.6	27 ± 8
51.2	81 ± 3
102.4	100 ± 0

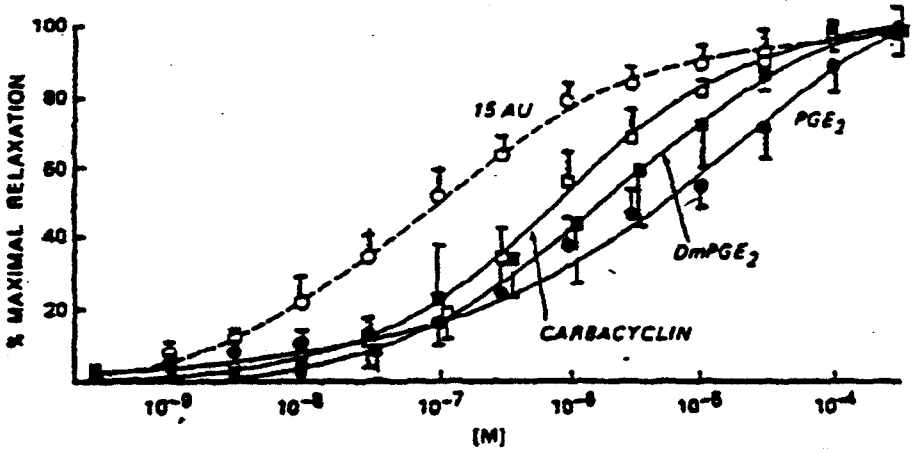
Results, expressed as % inhibition of control aggregation, are mean ± S.E.M. of 3 experiments.

In vitro studies using human platelet-rich plasma showed that UT-15 [2.56 to 256 nM (1-100 ng/ml] also caused a concentration-dependent inhibition of ADP-induced aggregation of human platelets, with an IC_{50} of 28.2 nM (11 ng/ml). It is stated that UT-15 was found to be 20-fold less potent than prostacyclin in inhibiting the ADP-induced aggregation of human platelets.

2. Vascular Relaxation Effect

UT-15 (1-1000 nM) produced a concentration-dependent relaxation of isolated rabbit mesenteric artery segments precontracted with the thromboxane mimetic U-46619 (1 μM; Figure 1), the order of potency (when compared to other prostaglandins) being UT-15 > carbacyclin (a stable prostacyclin analogue) > 16-dimethyl PGE_2 > PGE_2. In this study, UT-15 was found to be about 8 and 45 times more potent in inducing vascular relaxation than carbacyclin and PGE_2, respectively.

Figure 1.



Relaxant actions of PGE_2 (●, n = 6), 15AU81 (○, n = 6), 16-dimethyl PGE_2, $DmPGE_2$ (■, n = 4), and carbacyclin (□, n = 5), in rabbit mesenteric artery precontracted with 10^{-6}M U-46619, a thromboxane mimetic. Results, expressed as % maximum relaxations, are shown as Mean ± SEM.

3. Antiproliferative Effect in Human Pulmonary Artery Smooth Muscle Cells

UT-15 (30 nM for 48 hours) markedly reduced the proliferation of cultured human pulmonary artery smooth muscle cells, as measured by blinded cell counting (92% reduction) and [^{3}H] thymidine incorporation (61% reduction). Moreover, it was shown that UT-15 produced a large elevation (about 120 fold) in intracellular cAMP, which was still elevated (about 6 fold) 72 hours after drug treatment. The above results indicate that UT-15 exerts its antiproliferative effect via a cAMP-dependent pathway in pulmonary artery smooth muscle cells.

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