CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-038	**Code: 1S**
Name: [redacted]™ (Dexmedetomidine HCL) for Infusion	
Sponsor: Abbott Laboratories, 200 Abbott Park, Abbott Park, IL 60064	
Submission Type: Original NDA	**Submission Date:** December 18, 1998
Reviewer: Suresh Doddapaneni, Ph.D.	

SYNOPSIS

Dexmedetomidine is intended for alpha$_2$ sedation and analgesia in an intensive care setting (IC) and is claimed to produce titratable, predictable sedation, from which patients are easily arousable and cooperative.

Chiral inversion of dexmedetomidine to the inactive *levo* isomer is likely to be insignificant. Recovery of the radiolabel in the mass balance study was complete and quantitative. The excretion of the radioactivity was rapid with about 85% recovered in the urine within 24 hours post dosing. Dexmedetomidine undergoes complete biotransformation *in vivo* with very little excreted unchanged in the urine or feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. Direct N-glucuronidation to the inactive G-DEX-1 and G-DEX-2 conjugates accounts for about 34% of its metabolism. Aliphatic hydroxylation of dexmedetomidine (mediated primarily by CYP2A6) to generate 3-hydroxy dexmedetomidine, glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxy dexmedetomidine represents about 14% of the metabolism. N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for about 18% of the metabolism. Approximately, 28% of the urinary metabolites have not been identified. The average plasma protein binding of dexmedetomidine was 94%. The specific plasma protein to which dexmedetomidine binds is unknown.

Dexmedetomidine exhibits dose-independent pharmacokinetics in the dosage regimen (0.2 to 0.7 µg/kg/hr when infused up to 24 hours) proposed for the indication being sought. The main pharmacokinetic parameter values were consistent across several studies with varied infusion regimens (10 minute infusion, two-stage regimens (loading dose + maintenance dose), three-stage regimens (two loading doses + maintenance dose), and virtually continuously changing infusion rate regimens) and are as follows; The clearance is about 39.0 liter/hr, the terminal half-life is about 2 hours, and the steady state volume of distribution is about 1.3 liter/kg.

Dexmedetomidine did not show gender and age differences in pharmacokinetics of adult subjects. Therefore, based on pharmacokinetic considerations no dosage adjustments are warranted in females or in the elderly.

Dexmedetomidine pharmacokinetics were not affected in patients with severe renal impairment after a single dose administration of dexmedetomidine. No dosage adjustments are warranted based on the results from this study. However, the metabolites are completely excreted

in the urine and it is unknown if the metabolites accumulate when dexmedetomidine is infused continuously.

The pharmacokinetics of dexmedetomidine were affected in hepatic impairment requiring dosage adjustments when dexmedetomidine is used in this patient population. The mean CL values for subjects with mild, moderate, and severe hepatic impairment were only 74%, 64% and 53%, respectively, of those observed in the normal healthy subjects.

Based on *in vitro* metabolism studies, dexmedetomidine is not expected to inhibit the metabolism of drugs whose metabolism is mediated by CYP1A1, CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 isoforms. *In vivo* interaction studies showed that the pharmacokinetics of dexmedetomidine were not affected by the concurrent administration of alfentanil, midazolam, propofol, and isoflurane. *In vivo* interaction studies also showed that the pharmacokinetics of propofol, midazolam, and rocuronium were not affected by the concurrent administration of dexmedetomidine.

RECOMMENDATION

NDA 21-038 can be approved from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics provided a mutually acceptable language can be worked out on the clinical pharmacology section of the package insert. Comments 1-2 on page 23 of this review should be sent to the sponsor.

/S/ 1/27/99

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/S/ 10/99

CC:
NDA 21-038, HFD-170 (Division File, Samantha), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), Barbara Murphy (CDR).

APPEARS THIS WAY
ON ORIGINAL

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I. INTRODUCTION

Dexmedetomidine is a potent and highly selective α_2-adrenoceptor agonist (α_2:α_1 ratio of 1600:1). It is the [redacted] -separated from racemic medetomidine. Activation of alpha$_2$ receptors located in the sympathetic nerve endings inhibits the release of norepinephrine. Activation of postsynaptic receptors by alpha$_2$ agonists in the CNS leads to inhibition of sympathetic activity, decreases in blood pressure and heart rate, sedation, and relief of anxiety. Binding of agonists to alpha$_2$ adrenoceptors in the spinal cord produces analgesia.

Dexmedetomidine is intended for alpha$_2$ sedation and analgesia in an intensive care setting (IC) and is claimed to produce titratable, predictable sedation, from which patients are easily arousable and cooperative. It is claimed to be relatively free of side effects. Most common adverse events associated with its use have been hypotension, hypertension, and bradycardia which are expected extensions of its pharmacologic effect and have been easily managed. Similar proportions of patients have had therapy discontinued because of adverse events in the dexmedetomidine and placebo control groups (3%, 30/1148 dexmedetomidine; 3%, 24/817 placebo). Currently, dexmedetomidine HCl is not approved for marketing in any country.

II. INDICATIONS AND DOSAGE AND ADMINISTRATION AS STATED IN THE PROPOSED PACKAGE INSERT

Indications:

"[redacted] is an alpha$_2$ sedative with analgesic properties for use in an intensive care setting."

Dosage and Administration:

[redacted] should be administered using a controlled infusion device.

[redacted] can be individualized and titrated to the desired clinical effect. For adult patients, [redacted] is initiated with a loading dose of 1.0 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation and/or analgesia. In clinical studies, doses as low as 0.05 mcg/kg/hr have been used and infusions up to 24 hours have been studied."

III. PHYSICOCHEMICAL PROPERTIES & FORMULATION

Dexmedetomidine is a white or almost white, crystalline powder freely soluble in water with a pKa of 7.1. Dexmedetomidine HCl for Infusion (100 µg/mL as dexmedetomidine base) is presented as a sterile, aqueous solution in ampoules and vials with a pH of 4.5 to 7.0. This solution is preservative free and contains no additive or chemical stabilizers. This solution is further diluted with normal saline prior to intravenous infusion.

IV. DEXMEDETOMIDINE METABOLISM

i. Proposed metabolic pathway

Dexmedetomidine undergoes almost complete biotransformation. No unchanged dexmedetomidine was excreted in urine. Very little (less than 1%) dexmedetomidine was excreted in feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. Figure 1 shows the proposed metabolic pathway of dexmedetomidine. Direct N-glucuronidation to the inactive G-DEX-1 and G-DEX-2 conjugates accounts for about 34% of its metabolism. Aliphatic hydroxylation (mediated primarily by CYP2A6) of dexmedetomidine to 3-hydroxy dexmedetomidine followed by glucuronidation to 3-hydroxy dexmedetomidine glucuronide, and/or further oxidation to 3-carboxylic acid dexmedetomidine represents about 14% of the metabolism. N-methylation of dexmedetomidine followed by aliphatic hydroxylation to 3-hydroxy N-methyl dexmedetomidine, followed further by oxidation to 3-carboxy N-methyl dexmedetomidine, and/or glucuronidation to N-methyl O-glucuronide dexmedetomidine accounts for about 18% of the metabolism. The N-Methyl metabolite itself was a minor circulating component and was undetected in urine. There may be additional uncharacterized metabolites (approximately, 28% of the urinary metabolites have not been identified).

In vitro metabolism studies (using liver microsomes, microsomes containing cDNA-expressed CYP isoforms, and selective CYP2A6 monoclonal antibody) showed that CYP2A6 is the largest single contributor of the CYP mediated hydroxylation of dexmedetomidine. Other isoforms such as CYP1A2, CYP2E1, CYP2D6, and CYP2C19 may also play a role in the hydroxylation of dexmedetomidine (Inhibition by CYP2A6 selective inhibitors was incomplete). *In vitro* metabolism studies also showed that the IC_{50} values for inhibition potential of dexmedetomidine against the different cytochrome P450 isoforms are relatively high compared to the expected therapeutic plasma concentrations of dexmedetomidine. The upper limit of the anticipated therapeutic concentration range is 1.2 ng/mL, which is 0.0096 μM. Based on this, the sponsor is concluding that dexmedetomidine is not likely to inhibit the metabolism and alter the pharmacokinetics of coadministered drugs.

Table 1. IC_{50} values for inhibition potential of dexmedetomidine against the different cytochrome P450 isoforms.

Cytochrome P450 isoform	Substrate	IC_{50} (μM)
1A1	Ethoxyresorufin O-deethylase	2.7
1A2	Ethoxyresorufin O-deethylase	2.0
2A6	Coumarin 7-hydroxylase	70
2C19	S-mephenytoin 4-hydroxylase	3.3
2E1	Chlorzoxazone 7-hydroxylase	2.2
3A4	Testosterone 6β-hydroxylase	0.65
2D6	Dextromethorphan O-demethylase	1.8

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