HYDEX

(Dexmedetomidine Concentrate for Infusion 100 mcg/ml, 2 ml vial)

i. Name and Strength of Active Substance(s)

Each ml contains:

Dexmedetomidine Hydrochloride USP 118 mcg equivalent to	
Dexmedetomidine	100 mcg
Water for Injection USP	Q.S. to 1 ml

ii. Product Description

HYDEX (Dexmedetomidine Hydrochloride Injection) is a clear, colourless solution filled in a clear glass vial, when examined under suitable condition visibly; it is free from foreign particles. HYDEX (dexmedetomidine hydrochloride) injection is a sterile, nonpyrogenic ready to use solution suitable for intravenous infusion. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. HYDEX has a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2$ • HCl. The structural formula of dexmedetomidine hydrochloride is as under (figure 1).

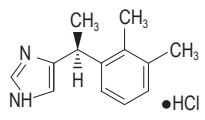

Figure 1. Dexmedetomidine

Description after dilution: A clear, colourless solution
HYDEX has been shown to be compatible when administered with the following intravenous fluids: 0.9% sodium chloride in water, 5% dextrose in water, 20% mannitol, Lactated Ringer's solution.

List of excipients
Sodium chloride
Water for Injection

iii. Pharmacodynamics/Pharmacokinetics

Pharmacodynamic Properties

Dexmedetomidine is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstricting effects prevail leading to an increase in systemic vascular resistance and blood pressure, while the bradycardic effect is further emphasised. Dexmedetomidine is relatively free from respiratory depressive effects when given as monotherapy to healthy subjects.

Pharmacokinetic Properties

The pharmacokinetics of dexmedetomidine has been assessed following short term IV administration in healthy volunteers and long term infusion in ICU population.

Distribution

Distribution half-life ($t_{1/2\alpha}$) of dexmedetomidine is about 6 minutes. The mean estimate of the terminal elimination half-life ($t_{1/2}$) is approximately 1.9 to 2.5 h (min 1.35, max 3.68 h) and the mean estimate of the steady-state volume of distribution (Vss) is approximately 1.16 to 2.16 l/kg (90 to 151 litres). Plasma clearance (Cl) has a mean estimated value of 0.46 to 0.73 l/h/kg (35.7 to 51.1 l/h). The mean body weight associated with these Vss and Cl estimates was 69 kg. Plasma pharmacokinetics of dexmedetomidine is similar in the ICU population following infusion >24 h. The estimated pharmacokinetic parameters are: $t_{1/2}$approximately 1.5 hours, Vss approximately 93 litres and Cl approximately 43 l/h. The pharmacokinetics of dexmedetomidine is linear in the dosing range from 0.2 to 1.4 µg/kg/h and it does not accumulate in treatments lasting up to 14 days. Dexmedetomidine is 94% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.85 to 85 ng/ml. Dexmedetomidine binds to both human serum albumin and Alpha-1-acid glycoprotein with serum albumin as the major binding protein of dexmedetomidine in plasma.

Biotransformation and Elimination

Dexmedetomidine is eliminated by extensive metabolism in the liver. There are three types of initial metabolic reactions; direct N-glucuronidation, direct N-methylation and cytochrome P450 catalysed oxidation. The most abundant circulating dexmedetomidine metabolites are two isomeric N-glucuronides. Metabolite H-1, N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide, is also a major circulating product of dexmedetomidine biotransformation. Cytochrome P-450 catalyses the formation of two minor circulating metabolites, 3-hydroxymethyl dexmedetomidine produced by hydroxylation at the 3-methyl group of dexmedetomidine and H-3 produced by oxidation in the imidazole ring. Available data suggest that the formation of the oxidised metabolites is mediated by several CYP forms (CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19). These metabolites have negligible pharmacological activity.

The major urinary metabolites are the two isomeric N-glucuronides, which together accounted for approximately 34% of the dose and N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide that accounted for 14.51% of the dose. The minor metabolites dexmedetomidine carboxylic acid, 3-hydroxymethyl dexmedetomidine and its O-glucuronide individually comprised 1.11 to 7.66% of the dose. Less than 1% of unchanged parent drug was recovered in the urine. Approximately 28% of the urinary metabolites are unidentified minor metabolites.

Special Populations

No major pharmacokinetic differences have been observed based on gender or age.

Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment. Subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C) had decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. Although dexmedetomidine is administered to effect, it may be necessary to consider initial/maintenance dose reduction in patients with hepatic impairment depending on the degree of impairment and the response.

The pharmacokinetics of dexmedetomidine in severe renal impairment (creatinine clearance <30 ml/min) is not altered.

Data in new-born infants (28 - 44 weeks gestation) to children 17 years of age are limited. Dexmedetomidine half life in children (1 months to 17 years) appears similar to that seen in adults, but in new-born infants (under 1 month) it appears higher. In the age groups 1 months to 6 years, body weight-adjusted plasma clearance appeared higher but decreased in older children. Body weight-adjusted plasma clearance in new-born infants (under 1 month) appeared lower (0.9 l/h/kg) than in the older groups due to immaturity.

iv. Indication

Intensive Care Unit Sedation

Hydex is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Hydex should be administered by continuous infusion not to exceed 24 hours.

Hydex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Hydex prior to extubation.

Procedural Sedation
Hydex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

v. Recommended Dosage

- Hydex dosing should be individualized and titrated to desired clinical response.
- Hydex is not indicated for infusions lasting longer than 24 hours
- Hydex should be administered using a controlled infusion device.

Dosage Information

Table 1. Dosage Information

Indication	Dosage and Administration
Initiation of Intensive Care Unit Sedation	**Initiation of Intensive Care Unit Sedation:** **For adult patients:** a loading infusion of one mcg/kg over 10 minutes **For patients over 65 years of age:** a dose reduction should be considered. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.
Maintenance of Intensive Care Unit Sedation	**For adult patients:** 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. **For patients over 65 years of age:** a dose reduction should be considered. **For patients with impaired hepatic or renal function:** a dose reduction should be considered
Initiation of Procedural Sedation	**For adult patients:** a loading infusion of one mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable. **For awake fiberoptic intubation patients:** a loading infusion of one mcg/kg over 10 minutes. **For patients over 65 years of age:** a loading infusion of 0.5 mcg/kg over 10 minutes. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.
Maintenance of Procedural Sedation	**For adult patients:** the maintenance infusion is generally initiated at 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. **For awake fiberoptic intubation patients:** a maintenance infusion of 0.7 mcg/kg/hr is recommended until the endotracheal tube is secured. **For patients with impaired hepatic or renal function:** a dose reduction should be considered.

Dosage Adjustment
Due to possible pharmacodynamic interactions, a reduction in dosage of Hydex or other concomitant anesthetics, sedatives, hypnotics or opioids may be required when co-administered.

Dosage reductions may need to be considered for patients with renal or hepatic impairment, and geriatric patients.

Preparation of Solution
Strict aseptic technique must always be maintained during handling of HYDEX. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
HYDEX must be diluted with 0.9% sodium chloride solution to achieve required concentration (4 mcg/mL) prior to administration. Preparation of solutions is the same, whether for the loading dose or maintenance infusion. To prepare the infusion, withdraw 2 mL of HYDEX Injection Concentrate, and add to 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Shake gently to mix well.

vi. Route of Administration

Intravenous infusion

vii. Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Advanced heart block (grade 2 or 3) unless paced.
- Uncontrolled hypotension.
- Acute cerebrovascular conditions.

viii. Warnings and Precautions

Monitoring

Hydex is intended for use in an intensive care setting, operating room and during diagnostic procedures. The use in other environments is not recommended. All patients should have continuous cardiac monitoring during Hydex infusion. Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea (see section xii).

The time to recovery after the use of dexmedetomidine was reported to be approximately one hour. When used in an outpatient setting close monitoring should continue for at least one hour (or longer based on the patient condition), with medical supervision continued for at least one further hour to ensure the safety of the patient.

General precautions

Dexmedetomidine should not be given as a bolus dose and in the ICU a loading dose is not recommended. Users should therefore be ready to use an alternative sedative for acute control of agitation or during procedures, especially during the first few hours of treatment. During procedural sedation a small bolus of another sedative may be used if a rapid increase in sedation level is required.

Dexmedetomidine normally does not cause deep sedation and patients may be easily roused. Dexmedetomidine is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

Dexmedetomidine should not be used as a general anaesthetic induction agent for intubation or to provide sedation during muscle relaxant use.

Dexmedetomidine lacks the anticonvulsant action of some other sedatives and so will not suppress underlying seizure activity.

Care should be taken if combining dexmedetomidine with other substances with sedative or cardiovascular actions as additive effects may occur.

Dexmedetomidine is not recommended for patient controlled sedation. Adequate data is not available.

When Dexmedetomidine is used in an outpatient setting patients should normally be discharged into the care of a suitable third party. Patients should be advised to refrain from driving or other hazardous tasks and where possible to avoid the use of other agents that may sedate (e.g, benzodiazepines, opioids, alcohol) for a suitable period of time based on observed effects of dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient.

Caution should be exercised when administering dexmedetomidine to elderly patients. Elderly patients over 65 years of age may be more prone to hypotension with the administration of dexmedetomidine, including a loading dose, for procedures. A dose reduction should be considered. Please refer to section v.

Cardio-vascular effects and precautions

Dexmedetomidine reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension (see section iii). Dexmedetomidine is therefore not suitable in patients with severe cardiovascular instability.

Caution should be exercised when administering dexmedetomidine to patients with pre-existing bradycardia. Data on the effects of Dexmedetomidine in patients with heart rate <60 are very limited and particular care should be taken with such patients. Bradycardia does not normally require treatment, but has commonly responded to anti-cholinergic medicine or dose reduction where needed. Patients with high physical fitness and slow resting heart rate may be particularly sensitive to bradycardic effects of alpha-2 receptor agonists and cases of transient sinus arrest have been reported.

The hypotensive effects of dexmedetomidine may be of greater significance in those patients with pre-existing hypotension (especially if not responsive to vasopressors), hypovolaemia, chronic hypotension or reduced functional reserve such as patients with severe ventricular dysfunction and the elderly and special care is warranted in these cases (see section vii). Hypotension does not normally require specific treatment but, where needed, users should be ready to intervene with dose reduction, fluids and/or vasoconstrictors.

Patients with impaired peripheral autonomic activity (e.g. due to spinal cord injury) may have more pronounced haemodynamic changes after starting dexmedetomidine and so should be treated with care.

Transient hypertension has been observed primarily during the loading dose in association with the peripheral vasoconstrictive effects of dexmedetomidine and a loading dose is not recommended in ICU sedation. Treatment of hypertension has generally not been necessary but decreasing the continuous infusion rate may be advisable.

Local vasoconstriction at higher concentration may be of greater significance in patients with ischaemic heart disease or severe cerebrovascular disease who should be monitored closely. Dose reduction or discontinuation should be considered in a patient developing signs of myocardial or cerebral ischaemia.

Caution is advised when administering dexmedetomidine together with spinal or epidural anaesthesia due to possible increased risk of hypotension or bradycardia.

Patients with hepatic impairment

Care should be taken in severe hepatic impairment as excessive dosing may increase the risk of adverse reactions, over-sedation or prolonged effect as a result of reduced dexmedetomidine clearance.

Patients with neurological disorders

Experience of dexmedetomidine in severe neurological disorders such as head injury and after neurosurgery is limited and it should be used with caution here, especially if deep sedation is required. Dexmedetomidine may reduce cerebral blood flow and intracranial pressure and this should be considered when selecting therapy.

Other

Alpha-2 agonists have rarely been associated with withdrawal reactions when stopped abruptly after prolonged use. This possibility should be considered if the patient develops agitation and hypertension shortly after stopping dexmedetomidine.

Dexmedetomidine may induce hyperthermia and in isolated cases temperatures ≥ 42°C have been reported. Hyperthermia can be resistant to traditional cooling methods. Dexmedetomidine treatment should be discontinued in the event of unexplained high fever. It is not recommended to use Dexmedetomidine in malignant hyperthermia-sensitive patients.

Dexmedetomidine contains less than 1 mmol sodium (23 mg) per ml.

ix. Interactions with Other Medicines and Other Forms of Interaction

Interaction studies have only been performed in adults.
Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, including sedative, anaesthetic and cardiorespiratory effects. Specific studies have confirmed enhanced effects with isoflurane, propofol, alfentanil, and midazolam.
No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with dexmedetomidine, a reduction in dosage of dexmedetomidine or the concomitant anaesthetic, sedative, hypnotic or opioid may be required.
Inhibition of CYP enzymes including CYP2B6 by dexmedetomidine has been studied in human liver microsome incubations. In vitro study suggests that interaction potential in vivo exists between dexmedetomidine and substrates with dominant CYP2B6 metabolism.
Induction of dexmedetomidine *in vitro* was observed on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4, and induction *in vivo* cannot be excluded. The clinical significance is unknown.
The possibility of enhanced hypotensive and bradycardic effects should be considered in patients receiving other medicinal products causing these effects, for example beta blockers, although additional effects in an interaction study with esmolol were modest.

x. Use during Pregnancy/Lactation

Pregnancy: There are no or limited amount of data from the use of dexmedetomidine in pregnant women. Studies in animals have shown reproductive toxicity. HYDEX is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation: Available data in the rat have shown excretion of dexmedetomidine or metabolites in milk. A risk to infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue dexmedetomidine therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility: In the rat fertility study, dexmedetomidine had no effect on male or female fertility.

xi. Effects on Ability to Drive and Use Machines

Patients should be advised to refrain from driving or other hazardous tasks for a suitable period of time after receiving Dexdor for procedural sedation.

xii. Adverse Effects/Undesirable Effects

Summary of the safety profile
The most frequently reported adverse reactions with dexmedetomidine are hypotension, hypertension and bradycardia.
Tabulated list of adverse reactions
Adverse reactions in Table 2 are ranked under headings of frequency, the most frequent first, using the following convention: Very common; common; uncommon; rare; very rare.

Table 2. Adverse reactions

Metabolism and nutrition disorders	
Common:	Hyperglycaemia, hypoglycaemia
Uncommon:	Metabolic acidosis, hypoalbuminaemia
Psychiatric disorders	
Common:	Agitation
Uncommon:	Hallucination
Cardiac disorders	
Very common:	Bradycardia
Common:	Myocardial ischaemia or infarction, tachycardia
Uncommon:	Atrioventricular block first degree, cardiac output decreased
Vascular disorders:	
Very common:	Hypotensio, hypertension
Respiratory, thoracic and mediastinal disorders	
Common:	Respiratory depression
Uncommon:	Dyspnoea, apnoea
Gastrointestinal disorders	
Common:	Nausea, vomiting, dry mouth
Uncommon:	Abdominal distension
General disorders and administration site conditions	
Common:	Withdrawal syndrome, hyperthermia
Uncommon:	Drug ineffective, thirst
Renal and urinary disorders	
Not known	*Polyuria*

xiii. Overdose and Treatment

Symptoms
Several cases of dexmedetomidine overdose have been reported both in the clinical trial and the post-marketing data. The reported highest infusion rates of dexmedetomidine in these cases have reached up to 60 µg/kg/h for 36 minutes and 30 µg/kg/h for 15 minutes in a 20-month-old child and in an adult, respectively. The most common adverse reactions reported in conjunction with overdose in these cases included bradycardia, hypotension, over sedation, somnolence and cardiac arrest.

Management
In cases of overdose with clinical symptoms, dexmedetomidine infusion should be reduced or stopped. Expected effects are primarily cardiovascular and should be treated as clinically indicated. At high concentration hypertension may be more prominent than hypotension. In clinical studies, cases of sinus arrest reversed spontaneously or responded to treatment with atropine and glycopyrrolate. Resuscitation was required in isolated cases of severe overdose resulting in cardiac arrest.

xiv. Incompatibilities

HYDEX infusion should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established.
HYDEX has been shown to be incompatible when administered with the following drugs: amphotericin B, diazepam.
HYDEX has been shown to be compatible when administered with the following intravenous fluids: 0.9% sodium chloride in water, 5% dextrose in water, 20% mannitol, Lactated Ringer's solution.
Compatibility with Natural Rubber: Compatibility studies have demonstrated the potential for absorption of HYDEX to some types of natural rubber. Although HYDEX is dosed to effect, it is advisable to use administration components made with synthetic or coated natural rubber gaskets.

xv. Shelf Life

Unopened vial:
3 years

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.
From a microbiological point of view, the product should be used immediately.

xvi. Storage Condition

Unopened vials
Do not store above 30 °C.

Diluted preparation
For storage conditions after dilution of the medicinal product, *see* Section xv: Shelf Life.

xvii. Instructions for Use

Strict aseptic technique must always be maintained during handling of HYDEX. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
HYDEX must be diluted with 0.9% sodium chloride solution to achieve required concentration (4 mcg/mL) prior to administration. Preparation of solutions is the same, whether for the loading dose or maintenance infusion. To prepare the infusion, withdraw 2 mL of HYDEX Injection Concentrate, and add to 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Shake gently to mix well.
HYDEX has been shown to be compatible when administered with the following intravenous fluids: 0.9% sodium chloride in water, 5% dextrose in water, 20% mannitol, Lactated Ringer's solution.

xviii. Dosage Forms or Presentation

Clear siliconised glass vial sealed with rubber stopper and aluminium seal.
Pack size: 1 vial

xx. Name and Address of Product Licence Holder

Accord Healthcare Sdn Bhd (1035160 D)
26-6, Menara 1MK
Kompleks One Mont Kiara,
No 1, Jalan Kiara, 50480 Kuala Lumpur
Malaysia

xxi. Date of Revision of Package Insert

01.01.2019

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