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**MODULE 1 –ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION
NEOSTIGMINE METHYLSULFATE INJECTION USP 0.5mg/ml**

1.3.1 SUMMARY PRODUCT CHARACTERISTICS (SmPC)

1	Name of the Finished Medicinal Product:																
1.1	Product Name: Neostigmine Methylsulfate Injection USP 0.5mg/ml																
1.2	Strength : 0.5 mg/ml																
1.3	Pharmaceutical Form: Injection																
2	Qualitative and Quantitative Compositions:																
	<p>Qualitative Declaration: Active component INN Name: Neostigmine Methylsulfate</p> <p>Quantitative Declaration: Each ml contains: Neostigmine Methylsulfate USP....0.5 mg Water for Injection USP.....Q.S.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Sr. No.</th> <th style="text-align: center;">Content Name</th> <th style="text-align: center;">Quality Standard</th> <th style="text-align: center;">Qty in mg/ ml</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">1.</td> <td>Neostigmine Methylsulfate</td> <td style="text-align: center;">USP</td> <td style="text-align: center;">0.50 mg</td> </tr> <tr> <td style="text-align: center;">2.</td> <td>Glacial Acetic Acid</td> <td style="text-align: center;">USP</td> <td style="text-align: center;">q.s.</td> </tr> <tr> <td style="text-align: center;">3.</td> <td>Water for Injection</td> <td style="text-align: center;">USP</td> <td style="text-align: center;">q.s. to 1.00 ml</td> </tr> </tbody> </table> <p>USP: United States Pharmacopoeia</p>	Sr. No.	Content Name	Quality Standard	Qty in mg/ ml	1.	Neostigmine Methylsulfate	USP	0.50 mg	2.	Glacial Acetic Acid	USP	q.s.	3.	Water for Injection	USP	q.s. to 1.00 ml
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2.	Glacial Acetic Acid	USP	q.s.														
3.	Water for Injection	USP	q.s. to 1.00 ml														
3	Pharmaceutical Form: Injection A clear, colourless solution																
4	Clinical Particulars:																
4.1	<p>Therapeutic Indications:</p> <p>Neostigmine Methylsulfate Injection, USP is indicated for:</p> <ul style="list-style-type: none"> • The symptomatic control of myasthenia gravis when oral therapy is impractical. • The prevention and treatment of postoperative distention and urinary retention after mechanical obstruction has been excluded. <p>Reversal of effects of nondepolarizing neuromuscular blocking agents (e.g., tubocurarine, metocurine, gallamine or pancuronium) after surgery.</p>																
4.2	<p>Posology and Method of Administration</p> <p>DOSAGE AND ADMINISTRATION: Symptomatic Control of Myasthenia Gravis One mL of the 1:2000 solution (0.5 mg) IM or SC. Sub-sequent doses should be based on the individual patient's response.</p> <p>Prevention of Postoperative Distention and Urinary Retention One mL of the 1:4000 solution (0.25 mg) IM or SC as soon as possible after operation; repeat every four to six hours for two or three days.</p>																

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	<p>Treatment of Postoperative Distention One mL of the 1:2000 solution (0.5 mg) IM or SC, as required.</p> <p>Treatment of Urinary Retention One mL of the 1:2000 solution (0.5 mg) IM or SC. If urination does not occur within an hour, the patient should be catheterized. After the patient has voided, or the bladder has been emptied, continue the 0.5 mg injections every three hours for at least five injections.</p> <p>Reversal of Effects of Nondepolarizing Neuromus-cular Blocking Agents When Neostigmine Methylsulfate is administered IV, it is recommended that atropine sulfate (0.6 to 1.2 mg) also be given IV using separate syringes. Some authorities have recommended that the atropine be injected several minutes before the neostigmine methylsulfate rather than concomitantly.</p> <p>The usual dose is 0.5 to 2 mg Neostigmine Methylsulfate given by slow IV injection, repeated as required. Only in exceptional cases should the total dose of neostigmine methylsulfate exceed 5 mg. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. The optimum time for administration of the drug is during hyperventilation when the carbon dioxide level of the blood is low. It should never be administered in the presence of high concentrations of halothane or cyclopropane. In the presence of bradycardia, the pulse rate should be increased to about 80/min with atropine before administering Neostigmine Methylsulfate. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.</p>
<p>4.3</p>	<p>Contra-indications: Neostigmine Methylsulfate Injection is contraindicated in patients with known hypersensitivity to the drug. It is also contraindicated in patients with peritonitis or mechanical obstruction of the intestinal or urinary tract.</p>
<p>4.4</p>	<p>Special warning and precautions for use:</p> <p>WARNING Neostigmine Methylsulfate Injection should be used with caution in patients with epilepsy, bronchial asthma, bradycardia, recent coronary occlusion, vagotonia, hyperthyroidism, cardiac arrhythmias or peptic ulcer. When large doses of Neostigmine Methylsulfate Injection are administered, the prior or simultaneous injection of atropine sulfate may be advisable. Separate syringes should be used for the Neostigmine Methylsulfate and atropine. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.</p> <p>PRECAUTIONS General It is important to differentiate between myasthenic crisis and cholinergic crisis caused by overdosage of Neostigmine Methylsulfate Injection. Both conditions result in extreme muscle weakness but require radically different treatment.</p>

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<p>4.5</p>	<p>Interaction with other drugs, other forms of interactions: Neostigmine Methylsulfate Injection does not antagonize, and may in fact prolong, the Phase I block of depolarizing muscle relaxants such as succinylcholine or decamethonium. Certain antibiotics, especially neomycin, streptomycin and kanamycin, have a mild but definite nondepolarizing blocking action which may accentuate neuromuscular block. These antibiotics should be used in the myasthenic patient only when definitely indicated, and then careful adjustment should be made of the anti-cholinesterase dosage. Local and some general anesthetics, antiarrhythmic agents and other drugs that interfere with neuromuscular transmission should be used cautiously, if at all, in patients with myasthenia gravis; the dose of Neostigmine Methylsulfate may have to be increased accordingly.</p>
<p>4.6</p>	<p>Usage in pregnancy & Lactation Pregnancy Teratogenic Effects: Pregnancy Category C There are no adequate or well-controlled studies of Neostigmine Methylsulfate in either laboratory animals or in pregnant women. Neostigmine Methylsulfate should be given to a pregnant woman only if clearly needed. Nonteratogenic Effects-Anticholinesterase drugs may cause uterine irritability and induce premature labor when given IV to pregnant women near term. Lactation It is not known whether Neostigmine Methylsulfate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from Neostigmine Methylsulfate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.</p>
<p>4.7</p>	<p>Effects on ability to drive and operate machine: Not applicable</p>
<p>4.8</p>	<p>Undesirable effects: Side effects are generally due to an exaggeration of pharmacological effects of which salivation and fasciculation are the most common. Bowel cramps and diarrhea may also occur. The following additional adverse reactions have been reported following the use of either neostigmine bromide or neostigmine methysulfate. Allergic reactions and anaphylaxis, dizziness, convulsions, loss of consciousness, drowsiness, headache, dysarthria, miosis and visual changes, cardiac arrhythmias (including bradycardia, tachycardia, atrioventricular block and nodal rhythm). These have been predominantly noted following the use of the injectable form of Neostigmine Methylsulfate. Increased oral, pharyngeal and bronchial secretions, respiratory arrest and bronchospasm, rash and urticaria, nausea, emesis, flatulence and increased peristalsis, urinary frequency, arthralgia.</p>
<p>4.9</p>	<p>Overdose and special antidotes : Overdosage of Neostigmine Methylsulfate can cause cholinergic crisis, which is characterized by increasing muscle weakness, and through involvement of the muscles of respiration, may result in death. Myasthenic crisis, due to an increase in the severity of the disease, is also accompanied by extreme muscle weakness and may be difficult to distinguish from cholinergic crisis on a symptomatic basis. However, such differentiation is extremely</p>

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	<p>important because increases in the dose of Neostigmine Methylsulfate or other drugs in this class, in the presence of cholinergic crisis or of a refractory or “insensitive” state, could have grave consequences. The two types of crisis may be differentiated by the use of edrophonium chloride as well as by clinical judgment.</p> <p>Treatment of the two conditions differs radically. Whereas the presence of myasthenic crisis requires more intensive anticholinesterase therapy, cholinergic crisis calls for the prompt withdrawal of all drugs of this type. The immediate use of atropine in cholinergic crisis is also recommended.</p> <p>Atropine may also be used to abolish or minimize gastrointestinal side effects or other muscarinic reactions; but such use, by masking signs of overdosage, can lead to inadvertent induction of cholinergic crisis.</p>
5	Pharmacological Properties:
5.1	<p>Pharmacodynamic Properties: Pharmacotherapeutic Group (ATC Code) : N07AA01</p> <p>Neostigmine inhibits the hydrolysis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase at sites of cholinergic transmission. It enhances cholinergic action by facilitating the transmission of impulses across neuromuscular junctions. It also has a direct cholinomimetic effect on skeletal muscle and possibly on autonomic ganglion cells and neurons of the central nervous system (CNS). Neostigmine undergoes hydrolysis by cholinesterase and is also metabolized by microsomal enzymes in the liver. Protein binding to human serum albumin ranges from 15 to 25%. The clinical effects of neostigmine usually begin within 20 to 30 minutes after IM injection and last from 2.5 to 4 hours.</p>
5.2	<p>Pharmacokinetic Properties: Following IM administration, Neostigmine is rapidly absorbed and eliminated. In a study of five patients with myasthenia gravis, peak plasma levels were observed at 30 minutes, and the half-life ranged from 51 to 90 minutes. Approximately 80% of the drug was eliminated in urine within 24 hours; approximately 50% as the unchanged drug, and 30% as metabolites. Following IV administration, plasma half-life ranges from 47 to 60 minutes have been reported with a mean half-life of 53 minutes.</p>
5.3	<p>Preclinical Safety Data : Long-term animal studies have not been performed to evaluate the carcinogenic potential of neostigmine. Neostigmine methylsulfate was not mutagenic in an in vitro bacterial reverse mutation assay (Ames test).</p>
6.	Pharmaceuticals Particulars:
6.1	<p>List of Excipients: Glacial Acetic Acid USP Water for Injection USP</p>
6.2	Incompatibilities: Do not mix Neostigmine Injection with any other product.
6.3	Shelf life: 24 Months
6.4	<p>Special precautions for storage: Store below 30°C. Protect from light.</p>

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6.5	<p>Nature and contents of container:</p> <p>1 ml: Neostigmine Methylsulfate Injection USP 0.5mg/ml is packed in 1ml USP Type I glass ampoule with black ring. 5 such ampoules are packed in a blister. 5 such blisters are packed in a carton with pack insert.</p> <p>5 ml: Neostigmine Methylsulfate Injection USP 0.5mg/ml is packed in 5ml USP Type I glass ampoule with black ring. 5 such ampoules in blister packed in a carton with pack insert.</p>
6.6	<p>Special precaution for disposal : Not Applicable</p>
7	<p>Registrant: Marketing Authorisation Holder:</p> <p>M/s PHILLIPS PHARMACEUTICALS (NIGERIA) LTD. Address : Afprint Industrial Estate, Plot 122-132, Apapa Oshodi Expressway Lagos. Country : Nigeria. Telephone : +234 806761764 Fax : --- E-mail : ---</p> <p>Manufacturing Site Address:</p> <p>M/s THEMIS MEDICARE LIMITED Address : Sector 6 A, Plot No. 16,17& 18, IIE SIDCUL,HARIDWAR-249 403, Uttarakhand Country : India Telephone : 91-1334-239322/21 Telefax : 91-1334-239217 E-Mail : hwldgmtech@themismedicare.com</p>
8	<p>Date of Revision of the Text: Not Applicable</p>
9	<p>Dosimetry (if applicable): Not Applicable</p>
10	<p>Instruction for preparations of Radiopharmaceutical (if applicable): Not Applicable</p>