SUMMARY OF PRODUCT CHARACTERISTICS (Hydrocortisone sodium succinate for Injection BP)

1. Name, strength & dosage form of the medicinal product :

Hydrocortisone sodium succinate for Injection BP

Strength

100 mg

2. Qualitative and quantitative composition

Each vial contains Hydrocortisone Sodium Succinate
equivalent to hydrocortisone 100.0 mg

3.Dosage Form:

Dry powder for Injection for parentral use

4. Clinical particulars :

4.1 Therapeutic indications

Anti-inflammatory agent.

Hydrocortisone is indicated for any condition in which rapid and intense corticosteroid effect is required such as:

1.*Collagen diseases*

Systemic lupus erythematosus

2. *Dermatological diseases*

Severe erythema multiforme (Stevens-Johnson syndrome)

3.*Allergic states*

Bronchial asthma, anaphylactic reactions

4.*Gastro-intestinal diseases*

Ulcerative colitis, Crohn's disease

5.*Respiratory diseases*

Aspiration of gastric contents

4.2 Posology and method of administration

Hydrocortisone may be administered by intravenous injection, by intravenous infusion or by intramuscular injection, the preferred method for initial emergency use being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer-acting injectable preparation or an oral preparation.

Dosage usually ranges from 100 mg to 500 mg depending on the severity of the condition, administered by intravenous injection over a period of one to ten minutes. This dose may be repeated at intervals of 2, 4 or 6 hours as indicated by the patient's response and clinical condition.

In general high-dose corticosteroid therapy should be continued only until the patient's condition has stabilised - usually not beyond 48 to 72 hours. If hydrocortisone therapy must be continued beyond 48 to 72 hours hypernatraemia may occur, therefore it may be preferable to replace Hydrocortisone with a corticosteroid such as methylprednisolone sodium succinate as little or no sodium retention occurs.

Although adverse effects associated with high dose, short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

Patients subjected to severe stress following corticoid therapy should be observed closely for signs and symptoms of adrenocortical insufficiency.

Corticosteroid therapy is an adjunct to, and not a replacement for, conventional therapy.

In patients with liver disease, there may be an increased effect (see section 4.4) and reduced dosing may be considered.

Elderly patients: Hydrocortisone is primarily used in acute short-term conditions. There is no information to suggest that a change in dosage is warranted in the elderly.

However, treatment of elderly patients should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age and close clinical supervision is required (See Section 4.4).

*Paediatric population:*While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient than by age or body weight but should not be less than 25 mg daily (see Special warnings and special precautions for use).

Preparation of solutions: For intravenous or intramuscular injection prepare the solution aseptically by adding not more than 2 ml of sterile water for injections to the contents of one vial of Hydrocortisone 100 mg, shake and withdraw for use.

For intravenous infusion, first prepare the solution by adding not more than 2 ml of sterile water for injections to the vial; this solution may then be added to 100 ml -1000 ml (but not less than 100 ml) of 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

When reconstituted as directed the pH of the solution will range from 7.0 to 8.0 and the appearance of the solution is clear and colourless to almost colourless.

4.3 Contraindications

Hydrocortisone is contra-indicated:

- where there is known hypersensitivity to the active substance or any of the excipients listed in section 6.1
- in systemic fungal infection unless specific anti-infective therapy is employed.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

4.4 Special warnings and precautions for use

Warnings and Precautions:

1. A Patient Information Leaflet is provided in the pack by the manufacturer.
2. Undesirable effects may be minimised by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity (see Section 4.2).
3. Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. In patients who have received more than physiological doses of systemic corticosteroids (approximately 30 mg hydrocortisone) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids, but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 30 mg hydrocortisone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 160 mg hydrocortisone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be ***considered*** even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 160 mg hydrocortisone.
- Patients repeatedly taking doses in the evening.

4. Patients should carry 'Steroid Treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.
5. Corticosteroids may mask some signs of infection, and new infections may appear during their use. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised.
6. Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.
7. Exposure to measles should be avoided. Medical advice should be sought immediately if exposure occurs. Prophylaxis with normal intramuscular immuneglobulin may be needed.
8. Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.
9 The use of Hydrocortisone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculosis regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.
10. Rarely anaphylactoid reactions have been reported following parenteral Hydrocortisone therapy. Physicians using the drug should be prepared to deal with such a possibility. Appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of drug allergy.
11. Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see Section 4.8).
12. Hydrocortisone may have an increased effect in patients with liver diseases since the metabolism and elimination of hydrocortisone is significantly decreased in these patients.
13. Corticosteroid therapy has been associated with central serious chorioretinopathy, which may lead to retinal detachment.
14. There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.
15. Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.
16. Hypertrophic cardiomyopathy was reported after administration of hydrocortisone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

Special precautions

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

1. Osteoporosis (post-menopausal females are particularly at risk).
2. Hypertension or congestive heart failure.
3. Existing or previous history of severe affective disorders (especially previous steroid psychosis).
4. Diabetes mellitus (or a family history of diabetes).
5. History of tuberculosis.
6. Glaucoma (or a family history of glaucoma).
7. Previous corticosteroid-induced myopathy.
8. Liver failure or cirrhosis.
9. Renal insufficiency.
10. Epilepsy.
11. Peptic ulceration.
12. Fresh intestinal anastomoses.

13. Predisposition to thrombophlebitis.
14. Abscess or other pyogenic infections.
15. Ulcerative colitis.
16. Diverticulitis.
17. Myasthenia gravis.
18. Ocular herpes simplex, for fear of corneal perforation.
19. Hypothyroidism.
20. Recent myocardial infarction (myocardial rupture has been reported).
21. Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.
22. Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.
23. Hydrocortisone can cause elevation of blood pressure, salt and water retention and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.
24. Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 Interaction with Other Medicaments and Other Forms of Interaction that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.
Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.
Paediatric population: Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. The use of steroids should be restricted to the most serious indications.
Use in the elderly: The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.
Systemic corticosteroids are not indicated for, and therefore should not be used to treat traumatic brain injury or stroke because it is unlikely to be of benefit and may even be harmful. For traumatic brain injury a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A casual association with methylprednisolone sodium succinate treatment has not been established.
This medicinal product contains 0.3 mmol (6.2 mg) of sodium per vial of 100mg hydrocortisone. This means that sodium content has to be taken into consideration by patients on a controlled sodium diet for dose above 370 mg of hydrocortisone.

4.5 Interaction with other medicinal products and other forms of interaction

1. Convulsions have been reported with concurrent use of corticosteroids and ciclosporin. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse effects associated with the individual use of either drug may be more apt to occur.
2. Drugs that induce hepatic enzymes, such as rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.
3. Drugs which inhibit the CYP3A4 enzyme, such as cimetidine, erythromycin, ketoconazole, itraconazole, diltiazem and mibefradil, may decrease the rate of metabolism of corticosteroids and hence increase the serum concentration.
4. Steroids may reduce the effects of anticholinesterases in myasthenia gravis. The desired effects of hypoglycaemic agents (including insulin), anti- hypertensives and diuretics are antagonised by

corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.
5. The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.
6. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and non- steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in hypothrombinaemia.
7. Steroids have been reported to interact with neuromuscular blocking agents such as pancuronium with partial reversal of the neuromuscular block.

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs, however, hydrocortisone readily crosses the placenta.
Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate in man, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra- uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Breast-feeding

Corticosteroids are excreted in breast milk, although no data are available for hydrocortisone. Doses up to 160 mg daily of hydrocortisone are unlikely to cause systemic systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression, but the benefits of breastfeeding are likely to outweigh any theoretical risk.

Fertility

Corticosteroids have been shown to impair fertility in animal studies. Adverse effects on fertility in rats with corticosterone were observed in males only and were reversible (see section 5.3). The clinical relevance of this information is uncertain.

4.7 Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as syncope, vertigo, and convulsions are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

Since Hydrocortisone is normally employed on a short-term basis it is unlikely that side-effects will occur; however, the possibility of side-effects attributable to corticosteroid therapy should be recognised (see Section 4.4).
Undesirable effects are classified into the following categories, according to system organ class, MedDRA terminology and MedDRA frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000) and
Not known (frequency cannot be estimated from the available data).

Adverse Reactions table	
System organ Class	Frequency Not Known (Cannot be estimated from available data)
Infections and infestations	Infection masked; Opportunistic infection
Neoplasms benign, malignant and unspecified (including cy polyps)	Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy)
Immune system disorders	Hypersensitivity (including anaphylaxis and anaphylactoid reactions [e.g. bronchospasm, laryngeal oedema,

	urticaria]); May suppress reactions to skin tests
Blood and lymphatic system disorders	Leucocytosis
Endocrine disorders	Cushingoid; Pituitary-adrenal axis suppression; WITHDRAWAL SYMPTOMS - Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see section 4.4); A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight
Metabolism and nutrition disorders	Sodium retention; Water retention; Alkalosis hypokalaemic; Glucose tolerance impaired; Increased appetite; Weight increased
Psychiatric disorders	Affective disorders (such as irritable, euphoric, depressed and labile mood psychological dependence and suicidal thoughts); Psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia); Behavioural disturbances; Irritability; Anxiety; Sleep disturbances; Cognitive dysfunction including confusion and amnesia
Nervous system disorders	Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of hydrocortisone; Benign intracranial hypertension; Convulsions; Epidural lipomatosis
Eye disorders	Cataract subcapsular; Glaucoma; Exophthalmos; Increased intra-ocular pressure, with possible damage to the optic nerve; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease; Central serous chorioretinopathy
Cardiac disorders	Cardiac failure congestive (in susceptible patients); Myocardial rupture following a myocardial infarction; Hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders	Hypertension; Thrombosis including Thromboembolism

Respiratory, thoracic and mediastinal disorders	Hiccups; Pulmonary embolism
Gastrointestinal disorders	Peptic ulcer (with possible perforation and haemorrhage); Gastric haemorrhage; Pancreatitis; Abdominal distension; Oesophageal ulceration; Oesophageal candidiasis; Intestinal perforation; Dyspepsia; Nausea
Skin & subcutaneous tissue disorders	Petechiae; Telangiectasia; Ecchymosis; Skin atrophy; Skin striae; Skin hyperpigmentation; Skin hypopigmentation; Hirsutism; Acne; Hyperhidrosis
Musculoskeletal, connective tissue and bone disorders	Myopathy; Muscular weakness; Osteonecrosis; Osteoporosis; Pathological fracture; Growth retardation
Reproductive system and breast disorders	Menstruation irregular; Amenorrhoea
General disorders and administration site conditions	Impaired healing; Abscess sterile; Malaise
Investigations	Carbohydrate tolerance decreased; Increased insulin requirement (or oral hypoglycemic agents in diabetics); Blood potassium decreased; Nitrogen balance negative (due to protein catabolism); Urine calcium increased; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood alkaline phosphatase increased; Weight increased
Injury, poisoning and procedural complications	Spinal compression fracture; Tendon rupture (particularly of the Achilles tendon)

4.9 Overdose

There is no clinical syndrome of acute overdosage with Hydrocortisone. Hydrocortisone is dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids

ATC code: H02AB09

Hydrocortisone sodium succinate has the same metabolic and anti- inflammatory actions as hydrocortisone. It is a glucocorticosteroid. Used in pharmacological doses, its actions supress the clinical manifestations of disease in a wide range of disorders.

5.2 Pharmacokinetic properties

Twelve normal subjects received 100, 200 or 400 mg Hydrocortisone intravenously. Radio-immunoassay results were as follows:-

Dose (mg)	Cmax (mcg / 100 ml)	Tmax (h)	12-HR AUC (mg / 100 ml x h)
100	132.3	0.35	418.0
200	231.8	0.25	680.0
400	629.8	0.37	1024.0

In another study, a 1 mg/kg i.m. dose of Hydrocortisone peaked in 30-60 minutes, with a plasma cmax of 80 mg/100 ml.

In analysing hydrocortisone metabolism, a 25 mg IV dose resulted in higher plasma concentrations in females than in males.

5.3 Preclinical safety data

Hydrocortisone was not mutagenic in bacterial assays but induced chromosome aberrations in human lymphocytes in vitro and in mice in vivo. Hydrocortisone did not increase tumour incidences in male and female rats during a limited 2-year carcinogenicity study.

Corticosteroids have been shown to reduce fertility when administered to rats. Adverse effects on fertility in rats with corticosterone were observed in males only and were reversible. Decreased weights and microscopic changes in prostate and seminal vesicles were observed. The numbers of implantations and live fetuses were reduced and these effects were not present following mating at the end of the recovery period.

6. Pharmaceutical particulars

6.1 List of excipients :

Not Applicable

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Store at a temperature not exceeding 30^{o}C.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass vials closed by a bromobutyl rubber closure and capped with an aluminium flip cap

6.6 Special precautions for disposal and other handling

Instructions for reconstitution:

Hydrocortisone should be reconstituted by adding not more than 2ml of sterile Water for injections to the contents of one vial. A homogeneous solution will be obtained by shaking gently. The solution of the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. The formulation does not contain a preservative and is for single use only. Once opened, the content of a vial should normally be used immediately (see section 6.3).

For instructions on administration, see section 4.2.

For IV infusion, the following solutions can be used: dextrose 5% in water, isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

M/s. NCI Pharmchem Ind. Ltd.,
29, IGBEHINADUN Street,
OSHODI, LAGOS,
NIGERIA

8. Marketing authorisation number(s)

B4-2771

9. Date of first authorisation/renewal of the authorization

Not Applicable

10. Date of revision of the text

Not Applicable